Exhibit 2

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO:*** ***Gallardo v. Johnson & Johnson*, No. 3:18-cv-10840**	**MDL NO. 16-2738 (FLW) (LHG)**

EXPERT REPORT OF KEVIN HOLCOMB, MD, FACOG

Date: May 28, 2024

Kevin Holcomb

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Personal Background

Gynecologic oncologists are specialists in the treatment of women with gynecologic malignancies, including cancers of the ovary, uterus, cervix and other sites. It is the only area of oncology wherein one clinician is responsible for both the medical and surgical aspects of a patient's care, and this leads to a unique comprehensive model of cancer therapy. A gynecologic oncologist does not just comprehensively treat the cancer of the presenting patient but is also responsible for the identification of additional cancer risks for the patient and her family.

It was this uniqueness that I was immediately drawn to as a 4th-year medical student at New York Medical College. Upon graduation, I continued my training as an intern and resident in Obstetrics and Gynecology at The New York Hospital-Cornell Medical Center. Following this four-year experience, I attended a three-year fellowship training in Gynecologic Oncology at Downstate Medical Center/Kings County Hospital. This fellowship, approved by the American Board of Obstetrics and Gynecology ("ABOG"), focused on the study of the causes and treatments for all gynecologic malignancies. My fellowship training occurred in a safety-net hospital in Brooklyn, New York that cares largely for an African American and Afro-Caribbean patient population. This is a demographic with a significantly higher rate of genital talc use and yet a lower risk of ovarian cancer compared with Caucasian women. I was never taught that talc use is an accepted risk factor for gynecologic cancer, to routinely investigate its usage while obtaining a medical history, or to recommend against its use.

After completing my fellowship, I remained on the academic faculty at Downstate as an Assistant Professor until moving to Beth Israel Medical Center in Manhattan to become the Director of Gynecologic Oncology at that institution. I remained there for five years before returning to Weill-Cornell Medicine/New York-Presbyterian Hospital in 2006 as a member of the Gynecologic Oncology division and an Associate Professor at Weill Cornell Medical College. Since that time, I have been promoted to the positions of Director of Gynecologic Oncology, Vice-Chairman of Gynecology, and Director of Minimally Invasive Surgery in the Department of Obstetrics and Gynecology. From April to October of 2018, I was asked by the Dean of the Medical College to serve as the acting Chairman of the department during a nation-wide search and I am currently the Associate Dean of Admissions for the Weill-Cornell Medical College.

I presently practice in a division of five gynecologic oncologists, two nurse practitioners, one physician assistant, and the administrative and research support staff. Despite significant administrative and academic responsibilities, much of my time is spent in clinical practice. I have been fortunate to build a busy gynecologic oncology practice and have been named as a "Top Doctor in the New York Metropolitan Area" by Castle-Connelly Inc. since 2009. I have performed approximately 200 surgeries per year since the early 2000s and treat approximately 20 new ovarian cancer patients per year. In addition, I am responsible for the follow-up care and treatment of approximately 50 existing ovarian cancer patients per year. This includes managing the chemotherapy, immunotherapy, and targeted therapy of high-risk patients.

As previously mentioned, my clinical responsibilities also include assessing cancer risk in my patients and their families. This includes the identification of genetic, reproductive, and

environmental risk factors. While I routinely counsel patients about the impact of known cancer risk factors like cigarette smoking, Human Papilloma Virus (HPV) infection, and family cancer history, I do not inquire (and have never inquired) about prior talc use; nor do I recommend against it for my ovarian cancer patients. I know of no one in my division or specialty who does so, and this is in keeping with the recommendations of the professional societies, including the American College of Obstetricians and Gynecologists ("ACOG") and the Society of Gynecologic Oncology ("SGO") that offer practice guidelines for the specialty.

In 2010, we were approved by ABOG, in conjunction with our colleagues at Columbia Medical Center, to start a three-year gynecologic oncology fellowship training program. The clinical training and mentorship of ob/gyn residents and gynecologic oncology fellows is an aspect of my career that I find particularly satisfying. I have received numerous teaching awards throughout my career and was recognized by the Council on Residency Education in Obstetrics and Gynecology with the National Faculty Teaching Award in 2002 and 2004. We have graduated eleven solid gynecologic oncologists since our inception, and none has been trained to routinely inquire about or recommend against genital talc usage.

As a member of the gynecologic oncology division, I am also involved in shaping the research priorities of the division. We perform clinical, translational, and basic science studies within the department, and I have personally authored or co-authored more than 90 articles in the peer-reviewed literature. My current research interests include population-based outcomes analysis, evaluation of novel biomarkers in ovarian cancer, and translational research on the immune-biology of the ovarian cancer tumor microenvironment. I am the principal investigator for two multi-institutional prospective trials examining the role of the novel serum biomarker, HE4, in the early detection of ovarian cancer, and I recently published on autophagy inhibition as a novel vaginal biomarker for ovarian cancer detection. My division collaborates with scientists within the medical college, and we were involved in the research recently published in *Cell*[1] and *Nature*[2] that were the first to identify the endoplasmic reticulum stress response as an important cause of immunosuppression in the ovarian cancer tumor micro-environment. The ultimate goal of these studies is to identify effective tests for the early detection of ovarian cancer and its precursors as well as therapeutic targets for more effective therapy. In addition to my personal involvement with translational and clinical research, I also act as a reviewer of research submitted for publication to journals such as *Gynecologic Oncology*, *Journal of the American Medical Association*, and *Obstetrics and Gynecology*. In this role, I make recommendations regarding the appropriateness, originality, and validity of the submitted research based on assessment of the study design, statistical analysis and presentation of the findings.

I have always considered advocacy for my patients to extend beyond my role as a clinician. I served as a member of the Harlem Cancer Control Coalition and was a past president of the Board of Advisors for the American Cancer Society Harlem Office. Both organizations are dedicated to the eradication of health care disparities, particularly those impacting communities

[1] Cubillos-Ruiz J.R. *et al*. Tumorigenic and immunosuppressive effects on endoplasmic reticulum stress in cancer. *Cell* 2017; 168: 692-706.

[2] Song M. *et al*. IRE1α–XBP1 controls T cell function in ovarian cancer by regulating mitochondrial activity. *Nature* 2018; 562: 423-428.

of color. I presently sit on the Scientific Advisory Board of "TEAL," an ovarian cancer advocacy organization based in Brooklyn, NY. Since 2009, TEAL has provided more than 3 million dollars in research support to some of the most innovative researchers in the nation. I was humbled to be an honoree at the organization's "10 Years of Amazing" Gala in April 2018 at the Brooklyn Museum of Art. More recently, I was recognized in 2022 with the Anne Grant Advocacy Leadership Award by SHARE, a national nonprofit that supports and educates women with gynecologic and breast cancers.

Because of my extensive clinical experience in the treatment of ovarian cancer, my experience as a researcher in the area of gynecologic oncology, my role in the medical education of future gynecologic oncologists, and my role in ovarian cancer patient advocacy, I feel particularly qualified to offer my opinion that there are insufficient data to conclude that genital talc use increases the risk of ovarian, fallopian tube, or primary peritoneal cancer. Together, these cancers account for most gynecologic oncology mortalities in the United States annually and there is no effective screen for any of them. After years of study on the relationship between genital talc and ovarian cancer, and in contrast to the case of cervical cancer and HPV infection, there is no public health program dedicated to the eradication of genital talc use. Much of the debate on the role of genital talc use in the carcinogenesis of ovarian cancer remains in the realm of product liability. In presenting the clinical and scientific data that support my professional opinion, I hope to explain why this is the case.

Scope of Report

I was asked to review the relevant scientific literature to furnish an opinion as to whether perineal use of talcum powder can cause ovarian cancer as a general matter, and, specifically, whether it caused Anna Gallardo to develop ovarian cancer. I was also asked to review the opinions of plaintiffs' gynecologic oncology expert Dr. Judith Wolf and to render an opinion as to whether her general and specific causation opinions are supported by the scientific literature and relevant medical records. My opinions in this report are based on my education, my experience as a gynecologic oncologist and my review of the peer-reviewed published scientific literature. I hold all the opinions in this report to a reasonable degree of medical certainty. I am being compensated at the rate of $1,000 per hour for the time I have spent to provide expert opinions in this litigation.

Summary of Opinions

Several factors may increase the risk for developing epithelial ovarian cancer, including genetic predisposition and reproductive history, and certain environmental exposures. Women who have family members with a history of ovarian cancer are the most susceptible to developing the disease themselves. Other known risk factors, which may vary by histological subtype, include, among other things, nulliparity, infertility, use of hormone replacement therapy drugs, endometriosis and cigarette smoking. Plaintiffs' experts proffer the opinion that genital talc use can also cause ovarian cancer. The scientific literature – and in particular, prospective cohort studies, which are the best studies we have to evaluate potential human carcinogens – simply does not support that position. Rather, the best available science indicates that genital talc use is not associated with, much less does it cause, an increased risk of ovarian cancer. In addition,

plaintiffs' experts' hypotheses regarding biologic plausibility ignore a host of contradictory studies. Recent scientific developments – including a pooled cohort study that considered more women for a longer period of time than any prior study and found no association between talc and ovarian cancer – have further undermined plaintiffs' experts' opinions in this litigation.

Ovarian Cancer Background

Ovarian cancer has earned its reputation as the most feared gynecologic malignancy by patients and physicians alike. While it is a relatively rare disease with a cumulative lifetime risk of approximately 1.3%, it accounts for more cancer deaths in the United States every year than the remaining gynecologic malignancies combined. In 2024, an estimated 19,680 American women will be diagnosed with ovarian cancer, and an estimated 12,740 will die from it.[3] Due to the diversity of cell types that comprise the ovary and the pluripotent nature of the germ cells themselves, the ovary has the potential to develop many distinct histologic types of cancer. Historically, ovarian cancers have been divided into three histologic types based on the cell of origin: epithelial, sex cord-stromal, and germ cell cancers. Each type of ovarian cancer has a unique average age at diagnosis, risk of metastatic disease and mortality, and treatment algorithm. Epithelial ovarian cancer is, by far, the most common cell type and accounts for 90% of ovarian cancers.[4] Unfortunately, it is also the cell type with the highest chance of extra-ovarian metastases at the time of diagnosis. Approximately 75% of patients with epithelial ovarian cancer ("EOC") present with disease that has already spread to the upper abdomen and beyond.[5] This combination of advanced stage of disease at presentation and a natural history of increasing chemotherapy resistance explain the poor survival associated with EOC. When diagnosed at an early stage (I or II), patients can expect 80-90% survival. However, the overall survival at five years is a disappointing 30-40% for the majority of patients who present with advanced stage (III or IV) EOC. Epidemiological studies examining the relationship between talcum powder exposure and ovarian cancer have largely been limited to EOC, and I will restrict the remainder of my report to this specific type.

Epithelial Ovarian Cancer

EOC includes cancers of serous, mucinous, clear cell and endometrioid varieties. Historically, these cell types were commonly combined in clinical and pathologic studies of EOC; however, recent advances in genomics have led to an appreciation of the biological diversity among the various types. It is now well-accepted that the various types of EOC are associated with distinct genetic aberrations, clinical presentations, and even risk factors. For example, nearly all high-grade serous adenocarcinomas of the ovary harbor a mutation in a tumor suppressor gene TP53.[6] In contrast, mucinous adenocarcinomas of the ovary rarely carry this mutation, but 40-50%

[3] National Institutes of Health, SEER Cancer Stat Facts: Ovarian Cancer. National Cancer Institute. Bethesda, MD. https://seer.cancer.gov/statfacts/html/ovary.html (last visited May 13, 2024).

[4] Torre L.A. *et al*. Ovarian cancer statistics. *CA Cancer J Clin* 2018; 68(4): 284-296.

[5] Sethna K. *et al.* Cytoreductive Surgery and Intraperitoneal Chemotherapy for Advanced Epithelial Ovarian Cancer. Chapter 10 in *Management of Peritoneal Metastases-Cytoreductive Surgery, HIPEC and Beyond*. 2018: 221-252.

[6] Mullany L.K. *et al*. Wild-type tumor repressor protein 53 (TRP53) promotes ovarian cancer cell survival. *Endocrinology* 2012; 153(4): 1638-1648.

harbor a mutation in KRAS and approximately 19% carry a Her2 Neu mutation.[7] Clear cell and endometrioid adenocarcinomas of the ovary commonly arise from endometriosis (a benign gynecologic disorder in reproductive-age women). Even within the endometrioid variety, there are two biologically distinct tumor types: low-grade and high-grade. The majority of low-grade endometrioid carcinomas cases harbor β-catenin and KRAS mutations that are usually absent in high-grade tumors.[8,9] The biologic diversity of EOC is not limited to genetic alterations but can also be seen in the risk factors for the various histologic types. For example, cigarette smoking only increases the risk of mucinous carcinoma of the ovary but not the other histologic types.[10] The new appreciation for the complexity surrounding the genetic underpinnings and environmental risks for the various forms of EOC renders the theory that a single environmental exposure, such as talcum powder, could increase the risk for all types of EOC much more difficult to justify scientifically. Not surprisingly, the poorer quality studies suggesting a connection between talc exposure and EOC come to various, and often conflicting, conclusions regarding the association of talc and the various histologic types. The largest association with genital talc use was found with serous adenocarcinoma by Cook *et al*. (1997),[11] Chang and Risch (1997),[12] Cramer *et al*. (1999),[13] and Gertig *et al*. (2000).[14] In contrast, Harlow *et al*. (1992)[15] identified the largest association with endometrioid tumors, while Mills *et al*. (2004)[16] identified mucinous tumors as having the largest association.

Ovarian Cancer Risk Factors

The risk factors for the development of EOC can be divided into genetic predispositions, reproductive factors, and environmental factors. There is a strong familial component to the disease. A woman with two first-degree family members with a history of ovarian cancer has a 7% lifetime risk, increased from the baseline risk of approximately 1.3%.[17] The highest risks are seen among women who carry germ-line mutations in ovarian cancer predisposition genes. Mutations in the BRCA1 and/or BRCA2 tumor suppressor genes are causes of two of the most

[7] Perren T.J. Mucinous epithelial ovarian carcinoma. *Annals of Oncol* 2016; 27: i53-i57.

[8] Soyama H. *et al*. A pathological study using 2014 WHO criteria reveals poor prognosis of grade 3 ovarian endometrioid carcinomas. *In Vivo* 2018; 32: 597-602.

[9] Lim D. *et al*. Morphological and immunohistochemical reevaluation of tumors initially diagnosed as ovarian endometrioid carcinoma with emphasis on high-grade tumors. *Am J Surg Pathol* 2016; 40(3): 302-312.

[10] Soegaard M. *et al.* Different risk factor profiles for mucinous and nonmucinous ovarian cancer: results from the Danish MALOVA study. *Cancer Epidemiol Biomarkers Prev* 2007; 16(6): 1160-1166.

[11] Cook L.S. *et al*. Perineal powder exposure and the risk of ovarian cancer. *Am J Epidemiol* 1997; 145(5): 459-465.

[12] Chang S. & Risch H.A. Perineal talc exposure and risk of ovarian carcinoma. *Cancer* 1997; 79: 2396-2401.

[13] Cramer D.W. *et al*. Genital talc exposure and risk of ovarian cancer. *Int J Cancer* 1999; 81: 351-356.

[14] Gertig D.M., Hunter D.J., Cramer D.W. *et al*. Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst* 2000; 92(3): 249-252.

[15] Harlow B.L. *et al*. Perineal exposure to talc and ovarian cancer risk. Obstet Gynecol 1992; 80(1): 19-26.

[16] Mills P.K. *et al*. Perineal talc exposure and epithelial ovarian cancer risk in the central valley of California. *Int J Cancer* 2004; 112: 458-464.

[17] Toss A. *et al.* Hereditary ovarian cancer: not only BRCA 1 and 2 genes. *Biomed Res Int* 2015: 341723.

common ovarian cancer familial syndromes and are associated with lifetime risks of ovarian cancer as high as 44% and 17%, respectively.[18] While the risk of EOC in these patients is significantly increased, BRCA1 and BRCA2 mutations account for only approximately 15% of EOC cases.[19] Less common hereditary ovarian cancer syndromes are associated with mutations in DNA mismatch repair genes (Lynch Syndrome), P53 mutation (Li-Fraumeni Syndrome), and multiple other genes involved in the double-strand DNA breaks repair system, such as CHEK2, RAD51, BRIP1, and PALB2.[20] The number of genes potentially associated with an increased risk of ovarian cancer is continually expanding. It should be noted that even the hereditary syndromes are associated with distinct histologic types of EOC. BRCA1 or BRCA2 mutation-associated ovarian cancers are most often high-grade serous carcinomas, while Lynch Syndrome is most often associated with endometrioid adenocarcinoma.[21]

Reproductive factors associated with an increased risk of EOC are early menarche (first menses) and late menopause, nulliparity (never having given birth), infertility, endometriosis, and the use of hormone replacement therapy. Having children, breastfeeding and long-term use of oral contraceptives all decrease the risk of EOC.[22] The association of these observations with ovulation led to a theory that "incessant ovulation" increases the risk of ovarian cancer and factors that inhibit ovulation protect against the disease.

One environmental factor that has been associated with an increased risk of EOC is cigarette smoking (mucinous adenocarcinoma).[23] While plaintiffs' experts have also identified asbestos as a cause of ovarian cancer, it is important to note the conditions under which occupational asbestos exposure has been linked to ovarian cancer.[24] These scenarios include women in the United Kingdom involved in the production of asbestos-containing gas masks during and before World War II (Acheson *et al.*),[25] former employees of a now-closed asbestos cement factory in Casale Monferrato, Italy (Magnani *et al.*),[26] and Italian women working in the asbestos-textile

[18] Kuchenbaecker K.B. *et al*. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA* 2017; 317(23): 2402-2416.

[19] Torre L.A. *et al*. Ovarian cancer statistics. *CA Cancer J Clin* 2018; 68(4): 284-296.

[20] Toss A. *et al*. Hereditary ovarian cancer: not only BRCA 1 and 2 genes. *Biomed Res Int* 2015: 341723.

[21] Toss A. *et al*. Hereditary ovarian cancer: not only BRCA 1 and 2 genes. *Biomed Res Int* 2015: 341723.

[22] Garg P.P. *et al*. Hormone replacement therapy and the risk of epithelial ovarian carcinoma: a meta-analysis. *Obstet Gynecol* 1998; 92(3): 472-479; Lacey J.V. Jr. *et al*. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA* 2002; 288(3): 334-341; Mills P.K. *et al*. Hormone replacement therapy and invasive and borderline epithelial ovarian cancer risk. *Cancer Detect Prev* 2005; 29(2): 124-132.

[23] Faber M.T. *et al*. Cigarette smoking and risk of ovarian cancer: a pooled analysis of 21 case-control studies. *Cancer Causes Control* 2013; 24(5): 1-26.

[24] IARC Monograph. Arsenic, Metals, Fibres, and Dusts, Volume 100C, A Review of Human Carcinogens. 2012; 100(C): 11-465.

[25] Acheson E.D. *et al.* Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. *Br J Ind Med* 1982; 39(4): 344-348.

[26] Magnani C. *et al*. Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. *Occup Environ Med* 2008; 65(3): 164-170.

industry (Germani *et al.*).[27] Notably, at the time of several of these studies, pathological methods to accurately distinguish between ovarian cancer and peritoneal mesothelioma had not yet been developed. And even if it were true that talc products contain asbestos, there is no evidence to suggest that talc users would sustain asbestos exposure comparable to that of the women in these studies, as Dr. Wolf admits.[28] By contrast, epidemiological studies of women who were exposed to asbestos in environmental, rather than occupational, settings have not shown a statistically significant association with ovarian cancer.[29] A review paper recently noted that because the "observed statistical association between asbestos and ovarian cancer . . . is weak and inconsistent," "[f]urther scientific investigation is needed to clarify the causal association of asbestos and ovarian cancer."[30]

Talc and Epithelial Ovarian Cancer

The physical properties of talc, including anti-sticking, anti-caking, thickener, lubricant, carrier, and absorbency, explain its use in multiple commercial applications. Talc is utilized in the production of paint, polymers, paper, ceramics, animal feed, cosmetics, and pharmaceuticals. Occupational exposure to talc can occur from its mining and milling as well as from working in the multiple industries that use talc. Consumer exposure to talc typically occurs from the use of cosmetics, feminine hygiene products like body powders and sprays, and talc-containing pharmaceuticals. The patterns of use regarding feminine hygiene products have been explored in multiple studies that examined the association between these products and ovarian cancer. Dusting of the genital area with powder is the predominant pattern of use; however, alternative patterns of use exist, including storage of diaphragms in talc and dusting of sanitary napkins. Studies that have a high prevalence of body powder use for feminine hygiene have attempted to quantify the frequency and duration of use, as well as the single or combination of patterns of use. What is clear is that women who use body powder for feminine hygiene typically do it daily and that it is a behavior that begins in early adulthood. Most women who use talc in the perineal area start use at around 20 years old.[31]

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[27] Germani D. *et al*. Cohort mortality study of women compensated for asbestosis in Italy. *Am J Indus Med* 1999; 36(1): 129-134.

[28] Dep. of Judith Wolf, M.D. ("Wolf 4/25/24 Dep.") 53:22-54:6, Apr. 25, 2024 ("[Q.] Are you aware of any studies that have shown that there is an ovarian cancer risk associated with the amount of asbestos that Dr. Longo reports finding in talcum powder? . . . A. I'm not aware of studies that are done looking at that."); *id.* 67:8-14 ("[Q.] Are you aware of any studies that show an increased risk of developing ovarian cancer based on the level of asbestos that Dr. Longo reports as being in Johnson's Baby Powder or Shower to Shower? . . . A. I'm not aware of any studies looking at that.").

[29] Reid *et al.* Cancer incidence among women and girls environmentally and occupationally exposed to blue asbestos at Wittenoom, Western Australia. *Int J Cancer* 2008; 122(10): 2337-2344; Dalsgaard S.B. *et al.* A cohort study on cancer incidence among women exposed to environmental asbestos in childhood with a focus on female cancers, including breast cancer. *Int J Environ Res Public Health* 2022; 19(4): 2086.

[30] Slomovitz B. *et al.* Asbestos and ovarian cancer: examining the historical evidence. *Int J Gynecol Cancer* 2021; 31(1): 122-128.

[31] Cramer D.W. *et al*. The association between talc use and ovarian cancer. *Epidemiology* 2016; 27(3): 334-346; O'Brien K.M. *et al.* Douching and genital talc use: patterns of use and reliability of self-reported exposure. *Epidemiology* 2023; 34(3): 376-384.

The literature examining the association between the use of talc-containing feminine hygiene products and ovarian cancer includes a fairly large number of studies of various designs. It is important to note the strengths and weaknesses of each study design and that these factors have led to a generally accepted hierarchy (*see* Figure 1) used to judge the strength of study results and the confidence we should have in them.

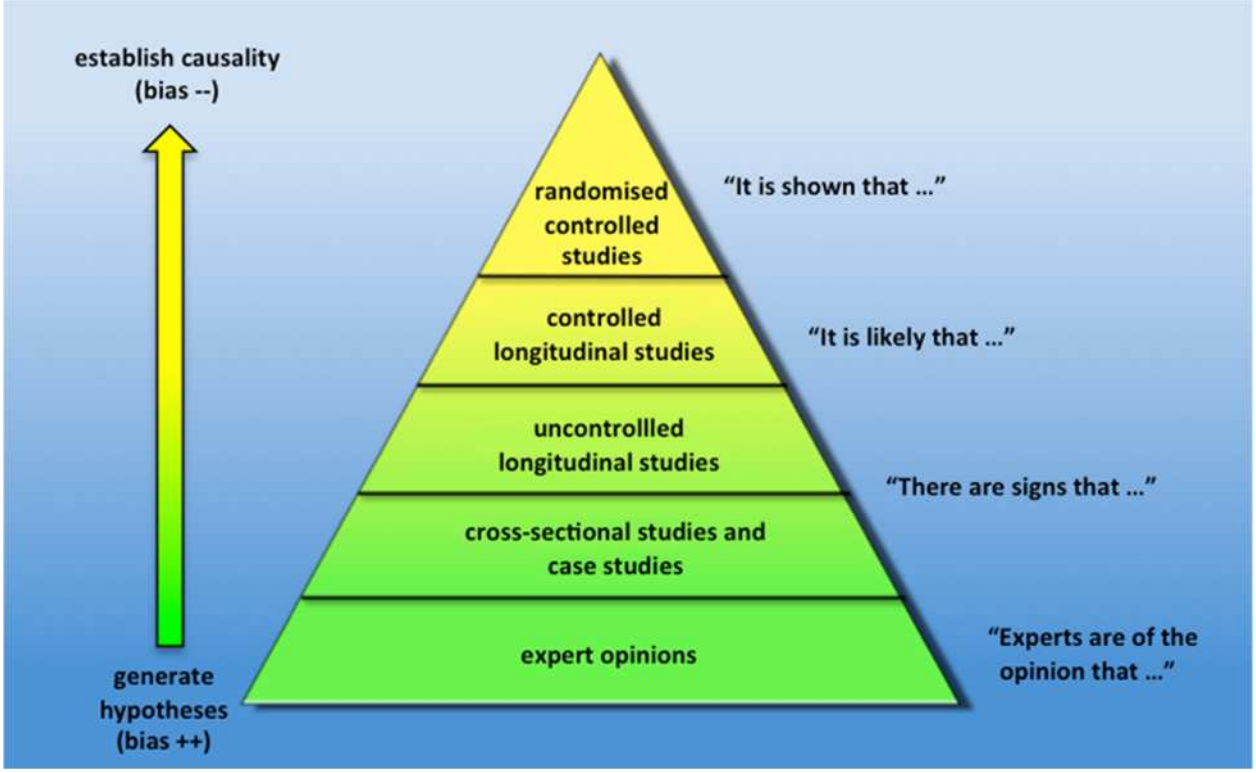

Figure 1. The Levels of Evidence. The Center for Evidence-Based Management[32]

The concept of "levels of evidence" was first described in a report by the Canadian Task Force on the Periodic Health Examination in 1979[33] in an effort to rate the strength of evidence behind various practice recommendations. This original rating system has been adapted multiple times over the years but remains essentially unchanged. It ranks study designs largely by their risk of bias and systematic errors that increase the likelihood of erroneous conclusions. Prospective randomized controlled trials (RCTs), where study participants are randomly assigned to a particular intervention or exposure and followed prospectively for the outcome of interest, are generally considered the highest level of evidence because they are designed to be unbiased. Obviously, for studies of potential human carcinogens, RCTs are not always feasible or ethical, and alternative study designs are often utilized. In general, prospective cohort (or "longitudinal") studies, where study participants are followed over years to determine the impact of a particular

[32] Center for Evidence-Based Management, What are the levels of evidence?. https://www.cebma.org/faq/what-are-the-levels-of-evidence/ (last visited May 13, 2024).

[33] The periodic health examination. Canadian Task Force on the Periodic Health Examination. *Can Med Assoc J* 1979; 121: 1193-1254.

exposure, are considered superior to retrospective case-control (cross sectional) studies, where study participants with a particular disease are retrospectively queried about a particular exposure and the results compared to a control population of individuals who do not have the disease. While retrospective case-control studies are less expensive to complete and require significantly less time compared with cohort studies, they are plagued by weaknesses that explain their lower position in the levels of evidence hierarchy. Recall bias is a systematic error where the recall of past exposures or experiences differs between the patients with (cases) and those without (controls) the specific disease of interest. Multiple factors have been shown to impact the level of accuracy of recall of an exposure, including time since the exposure, the level of detail requested, personal characteristics such as educational level and socioeconomic status, and desirability of the recalled event/exposure.[34] Recall bias can lead to spurious results in case-control studies in a variety of clinical scenarios.[35] For these reasons, prospective cohort studies have more ability to accurately detect an association between an exposure and a particular disease. While case-control studies may generate hypotheses, their findings should ultimately be confirmed in a prospective manner. It should also be noted that combining the data from multiple studies that are potentially plagued with bias, like what is done in a meta-analysis, cannot overcome the inherent weaknesses of the original studies. The risk of an erroneous conclusion due to biased data persists.

The statement by Dr. Wolf that epidemiological data show "a consistent, replicated, and statistically significant increase" in risk, is easily disproven.[36] As I explain in the following section, no prospective cohort study with long-term follow-up has shown an increased risk of ovarian cancer associated with cosmetic talc use. To the contrary, a 2020 pooled cohort study – the largest and most robust to date – found no association between ovarian cancer and cosmetic talc use. Moreover, roughly half of the retrospective case-control studies have come to the same conclusion. The erroneous conclusion that cosmetic talc use increases the risk of ovarian cancer can only be reached by a selective reading of the body of literature on the topic and abandoning the well-accepted hierarchy defining the strength of the various study designs. A non-biased review of the epidemiology also explains why the United States Food and Drug Administration, which regulates talc use in the U.S., reviewed the body of literature evaluating a potential association between talcum powder and ovarian cancer and concluded that "these studies have not conclusively demonstrated such a link, or if such a link existed, what risk factors might be involved."[37] Other governmental and medical institutions have reached similar conclusions.[38]

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[34] Coughlin S.S. Recall bias in epidemiological studies. *J Clin Epidemiol* 1990; 43(1): 87-91.

[35] Schildkraut J.M. *et al*. Association between body powder use and ovarian cancer: the African American cancer epidemiology study (AACES). *Cancer Epidemiol Biomarkers Prev* 2016; 25(10): 1411-1417.

[36] Second Amended Expert Report of Judith Wolf, M.D. ("Wolf MDL Report") at 10, Nov. 15, 2023.

[37] Food and Drug Administration. Talc. U.S. Department of Health and Human Services. http://www.fda.gov/Cosmetics/ProductsIngredients/Ingredients/ucm293184.htm (last updated Apr. 5, 2024).

[38] PDQ Screening and Prevention Editorial Board. Ovarian, Fallopian Tube, and Primary Peritoneal Cancers Prevention (PDQ)—Health Professional Version. National Cancer Institute. Bethesda, MD. https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq (last updated Mar. 6, 2024) ("Results from case-control and cohort studies are inconsistent, so the data are inadequate to support an association between perineal talc exposure and an increased risk of ovarian cancer."); IARC Monograph. Carbon Black, Titanium Dioxide, and Talc, Volume 93. 2010; 93: 1-413, pgs. 412-413 (noting "limited evidence" of carcinogenic potential for perineal use of

Human Studies on Cosmetic Talc Exposure

Case-Control Studies

The first retrospective case-control study to implicate the use of talc-containing feminine hygiene products in the future development of ovarian cancer was published in 1982 by Cramer *et al*.[39] The impetus for the study was the fact that talc was considered chemically similar to asbestos, which is known to cause mesothelioma, and the belief that talc applied to the genital area could be transported to the ovaries by passing through the uterus and fallopian tubes. In this study, 215 Boston-area white women with a history of EOC were compared with 215 controls (matched for age, ethnicity, and precinct of residence) with regard to their self-reported history of genital talc exposure. Two predominant modes of hygienic exposure to talcum powder were identified: use of talc as a dusting powder on the perineum and use of talc on sanitary napkins. Women who reported "any" prior use of genital talc were found to have a 92% increased risk of EOC compared with women reporting no prior exposure. Interestingly, women reporting use of talc by only one mode of exposure – dusting powder or on sanitary napkins – had only a borderline significant increased risk of EOC compared with controls. The weaknesses of this study design and the risk of unintended bias have already been addressed.

Since publication of the original Cramer study, there have been numerous case-control studies examining the relationship between any genital talc use and the risk of EOC. Table 1 provides a summary of these studies and demonstrates that roughly half show no significant increased risk for EOC associated with any genital talc use. It should be noted that in the studies that show a significantly increased risk, the risk estimates for any genital talc use and ovarian cancer are low and typically range between 1.2 and 1.6 (suggesting a 20%- 60% increased risk). Given that the odds ratios are so low, these results are unreliable and are likely nothing more than chance or the result of bias. Indeed, it has been well-documented that the existence of "over-reporting" and "recall bias for genital talc use among ovarian cancer survivors" in case-control studies must be accounted for in considering findings of positive associations.[40]

talcum powders in humans); Fiume M.M. *et al*. Safety Assessment of Talc as Used in Cosmetics. *International Journal of Toxicology* 2015; 34: 66S-129S (Cosmetic Ingredient Review concluded that talc was "safe for use in cosmetics in the present practices of use and concentration").

[39] Cramer D.W. *et al*. Ovarian cancer and talc: a case-control study. *Cancer* 1982: 50(2): 372-376.

[40] O'Brien K.M. *et al.* Douching and genital talc use: patterns of use and reliability of self-reported exposure. *Epidemiology* 2023; 34(3): 376-384; Whelan E. *et al.* Risk factors for ovarian cancer: an umbrella review of the literature. *Cancers* 2022; 14(11): 2708 ("Case-control studies are susceptible to recall bias, which has driven our main analysis to include cohort studies only."); Goodman J.E. *et al.* A critical review of talc and ovarian cancer. *J of Toxicology and Environmental Health, Part B* 2020; 23(5): 188-213 ("[T]he influence of recall bias could not be ruled out for case-control studies."); Wentzensen N. & O'Brien K.M. Talc, body powder, and ovarian cancer: a summary of the epidemiologic evidence. *Gynecologic Oncology*. 2021; 163(1): 199-208 ("Differential recall bias has been observed in case control studies for a wide range of exposures, but there are specific and well-documented concerns that differential recall bias underlies some of the associations in case-control studies of talc use and ovarian cancer risk.").

Prospective Cohort Studies

The first prospective cohort study to evaluate the risk of EOC associated with genital talc use was published by Gertig *et al*. in 2000.[41] This study included participants of a large study called the Nurses' Health Study ("NHS") that began in 1976 and prospectively followed 121,700 female registered nurses ranging in age from 30-55 years. Participants were sent questionnaires every two years that requested information about their medical history and risk factors for several diseases, including cancer and cardiovascular disease. In 1982, participants were queried about their history and frequency of application of body powder to the genital (perineal) area and/or application to sanitary napkins. The questionnaire specified frequency as none, daily, one to 6 days per week, and less than weekly. Seventy-eight thousand six hundred and thirty (78,630) women who responded comprised the study group. Forty percent of the respondents reported any use of talc in 1982, with 14.5% reporting daily use. Between 1982 and 1996, 307 women reported developing EOC and the diagnosis was confirmed by review of the medical records by a health care professional blinded to the exposure status of the participant. Overall, there was no significant increased risk of EOC seen in women reporting any use of talc for perineal dusting or application to sanitary napkins (relative risk 1.09, 95% confidence interval .86-1.37), and there was no increased risk of EOC seen in women with increasing frequency of applications (e.g., no dose-response relationship). Dr. Wolf testified that given the challenges of assessing dose, the evaluation of dose-response in the epidemiology was not as important to her analysis,[42] but the fact that one cannot accurately assess dose does not diminish its importance in the assessment of causality. A modest increased risk was seen for the development of invasive serous ovarian cancer in women reporting any use of talc (relative risk 1.4, 95% confidence interval 1.02-1.91) and a borderline significant trend was seen for increasing risk and increasing frequency of use.

In 2010, Gates *et al*. reported a longer-term follow up of the NHS cohort utilized in the original Gertig study.[43] The purpose of this subsequent study was to evaluate the risk factors for the specific histologic types of EOC. Follow-up of participants through 2006 (10 years longer than the original study by Gertig *et al*.) was high and included more than 95% of participants. Overall, the study findings supported the concept that the various histologic types of EOC carry distinct reproductive and environmental risk factors. Importantly, there was no increased risk of serous carcinoma associated with genital talc use seen, clarifying the finding of the only prospective cohort study reporting an association between genital talc use and EOC.

Houghton *et al*. utilized the Women's Health Initiative ("WHI") participants to examine perineal powder use and the risk of ovarian cancer.[44] The WHI was a large prospective study that enrolled more than 93,000 post-menopausal women aged 50-79 between 1993 and 1998. Participants were mailed annual questionnaires that collected information on risk factors and outcomes, including ovarian cancer. After applying appropriate exclusions, the final study population was

[41] Gertig D.M., Hunter D.J., Cramer D.W. *et al*. Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst* 2000; 92(3): 249-252.

[42] Dep. of Judith K. Wolf, M.D. ("1/7/19 Wolf Dep.") 332:15-333:9, Jan. 7, 2019.

[43] Gates M.A. *et al*. Risk factors for epithelial ovarian cancer by histologic subtype. *Am J Epidemiol* 2010; 171(1): 45-53.

[44] Houghton S.C. *et al*. Perineal powder use and risk of ovarian cancer. *J Natl Cancer Inst* 2014; 106(9): dju208.

comprised of 61,576 participants and 429 incident ovarian cancers that developed over a mean follow-up of 12.4 years. Use of genital talc was assessed at baseline with the question, "Have you ever used powder on your private parts (genital areas)?" Respondents responding yes were then asked to identify their duration of use (less than 1 year, 1-4 years, 5-9 years, 10-19 years, or >20 years). Similar assessments were done for women reporting use on a diaphragm and those reporting use on sanitary napkins or pads. Approximately half of the study population reported ever using perineal talc (52.6%), and there was no statistically significant association between the use of genital talc and the development of ovarian cancer for ever-users (HR 1.13; CI 0.93,1.37). The use of powder on sanitary napkins or diaphragms was also not associated with an increased risk of ovarian cancer. Dr. Wolf takes issue with the short follow-up period of the study;[45] however, there was no association with the duration of use and the future development of ovarian cancer and no increased risk for women who reported genital use of talc for 20 years or more (HR 1.10; CI 0.82,1.48). Women were also followed for a mean of 12.4 years after reporting use of talc for 20 years or more. Finally, a subset analysis showed no significantly increased risk specifically for serous adenocarcinoma in women reporting any use of perineal powder (hazard ratio 1.16, 95% CI .88,1.53).

The Sister Study, a prospective cohort study that examined the potential relationship between genital talc use and ovarian cancer, was published by Gonzalez *et al*. in 2016.[46] This study was started in 2003 and prospectively followed 41,654 women aged 35 to 74 in the US and Puerto Rico. Each participant had no prior breast cancer but had a full or half-sister with a history of breast cancer. Upon study entry, each participant was queried about reproductive history, health conditions and the use of personal care products (including use of perineal powders and sprays as well as douching) over the 12 months prior to enrollment. Information on the frequency of use was stratified as none, less than twice per month, 1-3 times per month, or more than 5 times per week. Follow-up questionnaires were administered every two years through 2009 and updated information on any cancers that developed. The risk for the development of EOC was calculated for talc exposure exclusively, douching exclusively, and for the combination of both exposures. During a median follow up of 6.6 years, 154 participants reported a diagnosis of ovarian cancer. The results showed that douching, not perineal talc use, significantly increased the risk of ovarian cancer. The hazard ratio for talc and ovarian cancer was .73 (95% confidence interval .44-1.2), while the hazard ratio for douching and ovarian cancer was 1.8 (95% confidence interval 1.2-2.8).[47] With respect to the short follow-up in this study, one must consider that the women likely started their talc use years prior to enrollment in the study.[48]

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[45] 1/7/19 Wolf Dep. 288:19-289:4; Wolf MDL Report at 8.

[46] Gonzalez N.L. *et al*. Douching, talc use, and risk of ovarian cancer. *Epidemiology* 2016; 27(6): 797-802.

[47] A more recent paper that looked at the use of personal care products (PCPs) and development of hormone-sensitive cancers among women enrolled in the Sister Study similarly found no statistically significant association between perineal talc use and ovarian cancer, but did find a statistically significant association for douching. Chang C.J. *et al.* Use of personal care product mixtures and incident hormone-sensitive cancers in the Sister Study: A U.S.-wide prospective cohort. *Environmental Int* 2024; 183: 108298.

[48] Cramer D.W. *et al*. The association between talc use and ovarian cancer. *Epidemiology* 2016; 27(3): 334-346; Wu A.H. *et al*. African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic whites after

Interestingly, the Sister Study found that women who used talc were twice as likely to douche. This finding is significant because it identifies douching as a potential confounder that was not controlled for in most prior case-control studies. If douching increases the risk of ovarian cancer and women who use talc are also more likely to douche (as demonstrated in the Sister Study), a case-control study could easily identify an association between talc use and ovarian cancer when no causal relationship exists.[49] This would not be the first time this occurred in the epidemiology of human cancers. Since the end of the 1960s, Herpes Simplex Virus ("HSV") was thought to be the main cause of invasive cervical cancer, largely based on a series of case-control studies showing a significant association.[50,51] Fortunately, subsequent prospective studies demonstrated no significant association between HSV and cervical cancer[52] and improvements in the detection of Human Papilloma Virus ("HPV") led to its identification as the true cause of invasive cervical cancer.[53] In retrospect, the case-control studies that initially identified an association between Herpes Virus and cervical cancer were biased because they did not control for HPV infection. Had the scientific community persisted in its belief that HSV caused cervical cancer, it is unlikely that prophylactic HPV vaccines, which have the potential to save millions of lives worldwide, would have ever been developed.

O'Brien *et al.* is a 2020 pooled cohort analysis that examined the potential association between genital talcum powder use and ovarian cancer.[54] It pooled data from four cohort studies (NHS I and II, WHI, and the Sister Study) and included more than 250,000 women. This makes it the "largest study of this topic to date."[55] During a median follow-up of 11.2 years, and after excluding women with missing data, 2,168 participants reported a diagnosis of ovarian cancer, and 250,577 participants did not report a diagnosis. The principal findings of the study were that there was no statistically significant increase in risk of ovarian cancer among women who had ever used powder, women who frequently used powder, or women who were long-term powder users.[56] Although O'Brien did report a weak association among women with patent reproductive

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considering nongenetic risk factors and oophorectomy rates. *Cancer Epidemiol Biomarkers Prev* 2015; 24(7): 1094-1100.

[49] Chang C.J. *et al.* Use of personal care product mixtures and incident hormone-sensitive cancers in the Sister Study: A U.S.-wide prospective cohort. *Environmental Int* 2024; 183: 108298.

[50] Rawls W.E. *et al.* An analysis of seroepidemiological studies of herpes virus type 2 and carcinoma of the cervix. *Cancer Res* 1973; 33(6): 1477-1482.

[51] Nahmias A.J. *et al.* Antibodies to herpesvirus hominis types 1 and 2 in humans: II. Women with cervical cancer. *Am J Epidemiol* 1970; 91(6): 547-552.

[52] Vonka V. *et al.* Prospective study on the relationship between cervical neoplasia and herpes simplex type-2 virus. *Int J Cancer* 1984; 33(1): 61-66.

[53] Lehtinen M. *et al.* Herpes simplex virus and risk of cervical cancer: a longitudinal, nested case-control study in the nordic countries. *Am J Epidemiol* 2002; 156(8): 687-692.

[54] O'Brien K.M. *et al.* Association of powder use in the genital area with risk of ovarian cancer. *JAMA* 2020; 323(1): 49-59.

[55] O'Brien K.M. *et al.* Association of powder use in the genital area with risk of ovarian cancer. *JAMA* 2020; 323(1): 49-59; Gossett D.R. *et al.* Use of powder in the genital area and ovarian cancer risk. *JAMA* 2020; 323(1): 29-31.

[56] Whelan E. *et al.* Risk factors for ovarian cancer: an umbrella review of the literature. *Cancers* 2022; 14(11): 2708 ("We do not consider the evidence of [the] association [between talc and ovarian cancer] as robust, which is supported by a recent pooled analysis of four prospective cohort studies showing no association.").

tracts, this "association was not significantly different from that observed in women with nonpatent reproductive tracts."[57] Dr. Wolf suggests that this finding supports her causation opinions,[58] but this position is not credible. Dr. Wolf also criticizes the O'Brien analysis for including cohorts with different information on talcum powder usage patterns.[59] But differing approaches to ascertainment of exposure patterns appear throughout the literature and is not a unique criticism to the O'Brien pooled cohort analysis. The same is true in the meta-analyses of case-control studies cited by Dr. Wolf.

In the last few weeks, Dr. O'Brien and colleagues published an article using the women from the Sister Study cohort, but a primarily retrospective design based on the fourth follow-up questionnaire, which re-assessed talc exposure 8-16 years after the beginning of the study between 2017 and 2019.[60] This study has at least two significant weaknesses. First, because women who developed ovarian cancers during the study were queried about their talc usage prior to the cancer diagnosis, the study is subject to the same type of recall bias as the case-control studies. This is especially so given the timing of the follow-up questionnaire. Additionally, data on talc use were sometimes contradictory and often missing. In fact, more than a quarter of the initial survey respondents failed to answer the follow-up questionnaire, leading to a significant loss of information. In response to these shortcomings, the authors calculated the impact of prior talc exposure on ovarian cancer risk under a variety of hypothetical scenarios (models), imputing data for the women with missing or contradictory information. In the two models where study participants were considered unexposed to talc if they reported being unexposed at study entry, there was no increased risk of ovarian cancer associated with ever use of talc. An increased risk of ovarian cancer was associated with ever use of talc only in models that corrected for contradictory exposure information by considering women as exposed to talc if they reported exposure during follow-up but not at study entry. The resulting hazard ratio of 1.82 (95% confidence interval 1.36-2.43) using one of these models is much higher than in other studies that rely only on actual data collected. This study also suggested that douching was not associated with an overall increase in the risk of ovarian cancer, exactly the opposite of the findings in the earlier prospective arm of the Sister Study. Because this recent O'Brien study is inconsistent with many epidemiological studies that have been performed without resorting to imputed data, I give it little weight in my evaluation of the evidence.

Meta-analyses and Systematic Reviews

A meta-analysis is a systematic review of data, carried out under strict criteria, that pools the data from multiple studies for a single quantitative analysis. The technique can provide useful information by increasing the sample size available to study a particular clinical question, but unfortunately has multiple caveats regarding the conduct and interpretation that increase the possibility of misleading results. Even small deviations from the rules defining the conduct of a

[57] O'Brien K.M. *et al.* Association of powder use in the genital area with risk of ovarian cancer. *JAMA* 2020; 323(1): 49-59.

[58] Wolf MDL Report at 10.

[59] Wolf MDL Report at 10.

[60] O'Brien K.M. *et al.* Intimate care products and incidence of hormone-related cancers: a quantitative bias analysis. *Journal of Clinical Oncology* 2024; epub. ahead of print.

meta-analysis can have a profound impact on the validity of the conclusions, and this is why the technique is considered potentially powerful but remains controversial. There are four critical principles of meta-analyses that must be considered: identification and selection of the included studies, heterogeneity among the results of the included studies, availability of the information, and analysis of the data. Numerous meta-analyses have been performed examining the impact of genital talc exposure and the risk of ovarian cancer and have come to discrepant results.

Terry *et al*. published their pooled analysis examining the impact of genital powder use and ovarian cancer risk in 2013.[61] The study included data from eight case-control studies contributing a total of 8,525 ovarian cancer cases and 9,859 controls for the pooled analysis. The study found a modest increased risk of ovarian cancer associated with genital powder use (odds ratio 1.24, 95% confidence interval 1.15-1.33). Risk was increased for cancers of serous, endometrioid, and clear cell varieties. Interestingly, no relationship between the number of lifetime applications and risk of ovarian cancer was identified (i.e., no dose-response relationship), and there was no increased risk for women who reported only non-genital powder use. Despite this analysis being performed after the publication of two prospective cohort studies evaluating genital powder use and ovarian cancer risk (Gertig *et al*. and Gates *et al*.), neither of these studies was included in the analysis. This is because the analysis was restricted to studies from the Ovarian Cancer Association Consortium, a group founded in 2005 to validate promising genetic associations in epidemiologic studies of ovarian cancer. This represents an informative example of the "study selection bias" that plagues many meta-analyses and weakens confidence in the results. No explanation for the restriction was offered by the authors, and it is not mentioned as a weakness in the discussion section.

In 2018, Berge *et al*. published their meta-analysis evaluating genital use of talc and the risk of ovarian cancer.[62] The authors ultimately identified 24 case-control studies, three cohort studies and one pooled analysis of eight of the 24 case-control studies. Significant heterogeneity was identified between the case-control and cohort trials. When combining the studies of both designs together, the authors found a weak, but statistically significant, increased association between genital talc use and ovarian cancer (relative risk 1.22, 95% confidence interval 1.13-1.30). This association was limited to serous carcinoma and no association was noted for the other histologic types. The authors noted a weak trend in risk ratio with regard to increasing duration or frequency of talc use. When the case-control studies were separated from the prospective cohort trials, however, the significant association was found only in the case-control studies (relative risk 1.26, 95% confidence interval 1.17-1.35). The prospective cohort studies showed no association between genital talc and ovarian cancer (relative risk 1.02, 95% confidence interval 0.85-1.20). As mentioned earlier, combining the results of studies with significant heterogeneity between them into a single meta-analysis increases the likelihood of

[61] Terry K.L. *et al*. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev Res* 2013; 6(8): 811-821.

[62] Berge W. *et al*. Genital use of talc and risk of ovarian cancer: a meta-analysis. *Eur J Cancer Prev* 2018; 27: 248-257.

spurious results. For this reason, the authors cautioned that "[t]he heterogeneity of results by study design however, detracts from a causal interpretation of this association."[63]

One of the largest meta-analyses on which plaintiffs' experts rely in evaluating ovarian cancer and genital talc use is the study by Penninkilampi and Eslick.[64] The data extraction section of the publication states that Penninkilampi is the person who performed the data extraction, assessed the quality of the studies using the Newcastle-Ottawa Scale (NOS), and calculated the unadjusted ORs and CIs when not reported in the original publications. It should be noted that the lead author, Ross Penninkilampi, was a medical student at UNSW Australia when this analysis was performed. Some of the data extraction is simply wrong. For example, for Chen (1992), the authors report an OR of 3.90 (CI 1.43-10.60) (statistically significant); however, the actual paper reports an OR of 3.90 (CI 0.9-10.60) (not statistically significant).[65] In addition, Penninkilampi reports the range of NOS ratings of the included studies as ranging from 5/10 to 8/10 when the NOS has a maximum score of 9, not 10. The authors queried six electronic databases for observational studies with greater than 50 ovarian cancer cases and selected 24 case-control studies (13,421 ovarian cancer cases) and three prospective cohort studies (890 ovarian cancer cases) for the analysis. The authors found that "any" genital talc use was associated with an increased risk of ovarian cancer (odds ratio 1.31, 95% confidence interval 1.24-1.39) and that >3600 lifetime applications (approximately 10 years of daily use) were associated with a "slightly" increased risk of ovarian cancer than <3600 applications. This association was only seen in serous and endometrioid varieties of ovarian cancer. Not surprisingly, the association with any genital talc use and ovarian cancer was found exclusively in case-control studies and not in prospective cohort studies, although the authors report that a significant increase in the risk of serous ovarian cancer specifically was found in cohort studies (OR 1.25, 95% confidence interval 1.01-1.55).

I found this study particularly interesting because of the authors' focus on the medical-legal aspects of the study question. To justify the need for the study, the authors state, "the association between talc use and ovarian cancer takes on considerable relevance, as the pharmaceutical and consumer products company Johnson & Johnson has recently had damages levied to the total of US$717 million dollars against them in five law suits."[66] Also peculiar is the exclusion of the updated data from the NHS prospective cohort study by Gates *et al*.[67] that updated the findings of the initial study by Gertig *et al*. showing an increased risk of serous ovarian cancer with any talc use. Inclusion of this study would have certainly negated the reported finding of an increased risk of serous carcinoma in cohort studies and could have potentially impacted the results in general. While the Gates *et al*. study clearly met the inclusion criteria for the current meta-

[63] Berge W. *et al*. Genital use of talc and risk of ovarian cancer: a meta-analysis. *Eur J Cancer Prev* 2018; 27: 248-257.

[64] Penninkilampi R. & Eslick G.D. Perineal talc use and ovarian cancer: a systematic review and meta-analysis. *Epidemiology* 2018; 29: 41-49.

[65] Chen Y. *et al.* Risk factors for epithelial ovarian cancer in Beijing, China. *Int J Epidemiol* 1992; 21(1): 23-29.

[66] Penninkilampi R. & Eslick G.D. Perineal talc use and ovarian cancer: a systematic review and meta-analysis. *Epidemiology* 2018; 29: 41-49.

[67] Gates M.A. *et al*. Risk factors for epithelial ovarian cancer by histologic subtype. *Am J Epidemiol* 2010; 171(1): 45-53.

analysis and is of a stronger level of evidence than most included studies, its title was not identified by the search terms chosen by Penninkilampi and Eslick.[68] This is a clear example of "study identification bias," another deviation from the principles of meta-analyses that can lead to misleading results.

In 2019, Taher *et al.* published a meta-analysis that evaluated a total of 24 case-control studies, as well as three cohort studies.[69] The study reported an overall OR of 1.28 (95% confidence interval 1.20-1.37) for the genital use of cosmetic talc and ovarian cancer. However, the authors admit that just over half (54%) of the included case-control studies showed an increased risk of ovarian cancer and data from the cohort studies showed no statistically significant increase in risk of ovarian cancer for ever-users of genital talc (OR of 1.06, 95% confidence interval 0.9-1.25). The authors concluded that their analysis "indicates that perineal exposure to talc powder is a possible cause of ovarian cancer in humans."[70] I found it interesting that in applying the GRADE framework, which is used to rate the strength and quality of evidence, the Taher *et al.* analysis reported that "the evidence derived from the observational studies in this review was initially classified as being of low certainty within the GRADE framework; this was further downgraded to very low certainty in light of the risk of bias."[71]

In Davis *et al.* 2021, the authors pooled data on genital talc use from studies included in the Ovarian Cancer in Women of Arican Ancestry Consortium. The paper reported an overall OR of 1.32 with a CI of 1.17-1.48 for ever use of talcum powder. However, when divided into subgroups, there was no statistically significant increase in risk of ovarian cancer for African-American women (OR of 1.22 with a CI of 0.97-1.53) despite data suggesting African-American women have higher usage rates than White women. The authors also examined both frequency of use and duration of use and expressly concluded "there was not a dose-response relationship" using either proxy for exposure amount.[72]

In 2022, Woolen *et al.* published a meta-analysis that evaluated whether there is an association between "frequent" use of cosmetic talc and ovarian cancer.[73] Although the analysis reported a positive association between "frequent" cosmetic talc use and ovarian cancer (odds ratio 1.47, 95% confidence interval 1.31-1.65), there are a number of problems associated with this analysis

[68] Penninkilampi R. & Eslick G.D. Perineal talc use and ovarian cancer: a systematic review and meta-analysis. *Epidemiology* 2018; 29(1): 41-49.

[69] Taher K.M. *et al.* Critical review of the association between perineal use of talc powder and risk of ovarian cancer. *Reproductive Toxicology* 2019; 90: 88-101.

[70] Taher K.M. *et al.* Critical review of the association between perineal use of talc powder and risk of ovarian cancer. *Reproductive Toxicology* 2019; 90: 88-101.

[71] Taher K.M. *et al.* Critical review of the association between perineal use of talc powder and risk of ovarian cancer. *Reproductive Toxicology* 2019; 90: 88-101.

[72] Davis C.P. *et al.* Genital powder use and risk of epithelial ovarian cancer in the Ovarian Cancer in Women of African Ancestry Consortium. *Cancer Epidemiol Biomarkers Prev* 2021; 30: 1660-1668.

[73] Woolen S.A. *et al.* Association between the frequent use of perineal talcum powder products and ovarian cancer: a systematic review and meta-analysis. *J Gen Intern Med* 2022; 37(10); 2526-2532.

that call into serious question the reliability of its results.[74] The Woolen *et al.* authors[75] defined "frequent" use as use of talc products two or more times a week, but it is unclear why the authors selected this arbitrary definition of "frequent." The Woolen *et al.* meta-analysis also reported on only a subset of the unpublished data from the O'Brien *et al.* pooled cohort analysis that included women with intact fallopian tubes, and ten case-control studies.[76] It is interesting that the Woolen *et al.* authors included only unpublished data from O'Brien *et al.* for women with a patent reproductive tract because the Woolen *et al.* analysis did not describe any inclusion criterion related to patency of the reproductive tract, and none of the other 10 studies included in the analysis limited its subjects to just patent women. Due to the arbitrary limitations set on the included data, the Woolen *et al.* meta-analysis included 6,542 ovarian cancer cases and 66,876 women, resulting in a significantly smaller sample size than the O'Brien *et al.* pooled cohort analysis. I also found it noteworthy that the Woolen *et al.* authors conceded that the study has several additional limitations, including the selection of the highest talc use for "duplicate reports of the same subjects;" the exclusion of cohort studies that had frequent-use study participants but did not capture the information in a specific way; and confounders such as recall bias associated with the underlying 10 case-control studies.

Most recently in 2023, Lynch *et al.* published a systematic review of the association between talc and female reproductive tract cancers.[77] The authors performed an extensive search of the literature, relying most heavily on the United States Environmental Protection Agency's (EPA) protocol for systematic reviews conducted under the Toxic Substances Control Act (TSCA) and the Draft Handbook for the Integrated Risk Information System. They identified 40 primary studies that assessed exposure to talc and female reproductive cancer risks in humans (n = 36) and animals (n = 4). After weighing the available data in both lines of studies, Lynch *et al.* determined that there is "suggestive evidence of no association between perineal application of talcum powders and risk of ovarian cancer at human-relevant exposure levels."[78]

Overall, the meta-analyses offer little new information regarding the association between genital talc use and ovarian cancer. Some case-control studies suggest a modest increased risk of ovarian cancer, while the higher-level prospective-cohort studies uniformly do not. Adding them together does not alter this reality.

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[74] PDQ Screening and Prevention Editorial Board. Ovarian, Fallopian Tube, and Primary Peritoneal Cancers Prevention (PDQ)—Health Professional Version. National Cancer Institute. Bethesda, MD. https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq (last updated Mar. 6, 2024) ("[B]ecause of the structure of this analysis, the results [in Woolen *et al.*] should be interpreted with care.").

[75] One of the authors of Woolen *et al.* is Rebecca Smith-Bindman, a plaintiffs' expert in this litigation.

[76] PDQ Screening and Prevention Editorial Board. Ovarian, Fallopian Tube, and Primary Peritoneal Cancers Prevention (PDQ)—Health Professional Version. National Cancer Institute. Bethesda, MD. https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq (last updated Mar. 6, 2024) (Woolen et al. is a "meta-analysis of ten case-control studies and a highly selected subset analysis of one prospective cohort study.").

[77] Lynch H.N. *et al.* Systematic review of the association between talc and female reproductive tract cancers. *Front Toxicol* 2023; 5:1157761.

[78] Lynch H.N. *et al.* Systematic review of the association between talc and female reproductive tract cancers. *Front Toxicol* 2023; 5:1157761.

Health Canada

In April 2021, Health Canada published an assessment of potential health risks from talcum powder and concluded the evidence is "indicative" of a causal effect. As a gynecologic oncologist, I follow the guidance and advice of domestic governmental organizations, principally the FDA, CDC, and NIH in addition to American medical organizations like SGO, ACOG and the American Cancer Society. I rely on these American institutions, none of which agrees with plaintiffs' theory that perineal exposure to talcum powder causes ovarian cancer.

Regardless, there are multiple issues affecting the reliability of Health Canada's determination. First, while the assessment concedes that around half of all case-control studies show no significant association, the authors continue to press the conclusion that there is a high degree of consistency among the data. This fallacious consistency conclusion is further called into question by the completely divergent findings when comparing results from cohort and case-control studies. The existence of disparate conclusions when looking at hospital studies versus population studies also cannot be squared with the assessment's conclusions on consistency. Second, the report outlines the numerous limitations that underlie the case-control studies like sample size and recall bias but systematically weighs the findings from those studies. Third, additional Bradford Hill criteria were unsatisfied – biologic plausibility and dose response – but the authors downplay these gaps in reaching their overall causal conclusions. The fundamental disconnect between the analysis conducted and conclusions rendered lead me to favor the consensus of U.S. public health organizations (e.g., NIH and FDA).

The Talc Theory

While the available epidemiological data do not support a definitive association, much less a causal relationship, between talc exposure and ovarian cancer, an examination of the data surrounding the carcinogenic potential of talc is worthwhile. This includes questions regarding the ability of talc particles to reach the ovaries and peritoneal cavity, the modes by which this may happen, and the proposed mechanisms of how they initiate or promote cancer once there. Although Dr. Wolf opines – without citation to any study showing a relationship between inhalation of talc and ovarian cancer – that inhalation is a secondary route of exposure,[79] the epidemiologic data on talc do not support inhalation as associated with an increased risk of ovarian cancer. The case-control studies that suggest a modest increased risk of ovarian cancer with talc exposure do not show an increased risk with "body-only" use. As such, the viability of their theory depends on the ability of talc to ascend through the female genital tract.

Migration of Talc Particles

Dr. Wolf takes as a given that talc particles can ascend the female genital tract, when in fact, data from animal studies on this issue are inconsistent (indeed, IARC determined that the evidence of

[79] Wolf MDL Report at 11, 13. In fact, Dr. Wolf cites to Cramer *et al*. 2007, where the authors explicitly stated that "[w]e are not claiming that a causal relationship between ovarian cancer and talc use is proven for this case or in general." Cramer D.W. *et al*. Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. *Obst Gyn* 2007; 110(2): 498-501 (cited in Wolf MDL Report at 13).

retrograde talc transport is "weak").[80] For example, Wehner *et al*. placed talc directly into the upper vagina of sedated cynomolgus monkeys on 30 occasions over a 45-day period, and the authors were unable to detect the radiolabeled talc in the uterus or higher in any animal despite efforts to promote migration through unnatural positioning and the administration of oxytocin.[81] In contrast, Henderson *et al*. placed a suspension of talc particles into the vaginas and uteri of eight Sprague-Dawley rats and found talc particles in the ovaries of all the rats that received intrauterine talc injections and in the rats that received intravaginal instillations of talc and were sacrificed after four days.[82] Indeed, like Wehner and Henderson, almost all of the animal studies deposited talc deep into the internal reproductive tract. With regard to human studies, Heller *et al*. examined the ovaries of 24 women undergoing surgical removal of the ovaries, 12 of whom reported frequent use of genital talc products.[83] The presence of talc was examined by polarized light and electron microscopy. Interestingly, talc particles were found in all 24 women, regardless of talc exposure history, and particle counts were completely unrelated to reported levels of genital talc exposure. In fact, higher talc particle levels were found in women with no reported talc exposure. These findings call into question the mode of exposure of the ovaries to talc particles, raise the potential of contamination during specimen handling, and call into question the clinical significance of talc particles that may be identified in the pathologic specimens of patients with ovarian cancer. As noted by Dr. Wolf,[84] Cramer *et al*. identified talc particles in the pelvic lymph nodes of a 68-year-old woman with stage III ovarian cancer using polarized and electron microscopy.[85] Interestingly, the reported patient was stage III because of metastatic disease in her right pelvic nodes, and yet talc particles were only found in her left pelvic lymph nodes, which did not contain cancer. Dr. Wolf also mentions a handful of human studies that she claims show the transport of non-talc particles,[86] but those studies, too, uniformly involved insertion deep into the internal genitalia and the use of unnatural positioning or hormone treatment to promote migration.

Additionally, if ascension of talc particles through the female genital tract is essential in its ability to cause/promote ovarian cancer, one would expect a protective effect from procedures like tubal ligation or hysterectomy that block this mode of exposure. However, data are inconsistent as to whether tubal ligation has a protective effect, as demonstrated by multiple studies examining the association between genital talc use and ovarian cancer, including the

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[80] 1/7/19 Wolf Dep. 191:21-192:3; IARC Monograph. Carbon Black, Titanium Dioxide, and Talc, Volume 93. 2010; 93: 1-413, pg. 411.

[81] Wehner A.P. *et al*. On talc translocation from the vagina to the oviducts and beyond. *Food Chem Toxicol* 1986; 24(4): 329-338.

[82] Henderson W.J. *et al*. The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat. *Environ Research* 1986; 40: 247-250.

[83] Heller D.S. *et al*. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Am J Obstet Gynecol* 1996; 174: 1507-1510.

[84] Wolf MDL Report at 13.

[85] Cramer D.W. *et al*. Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. *Obst Gyn* 2007; 110(2): 498-501.

[86] Wolf MDL Report at 13.

prospective cohort study of the NHS participants (Gertig *et al.*)[87] as well as the meta-analysis by Terry KL *et al.*[88] In addition, some analyses limited to modes of exposure that ensure internal deposition of the talc particles, like dusting of diaphragms[89] or condoms[90] show no increased risk of ovarian cancer with these behaviors.

Talc and Ovarian Cancer Carcinogenesis

Talc has not proven genotoxic to normal cells, and there is speculation regarding just how it potentially causes cancer. One theory set forth by Dr. Wolf is that chronic inflammation caused by talc particles either initiates or promotes carcinogenesis.[91] Some in the published literature have raised similar possibilities. For instance, the recent article by O'Brien and colleagues raised the possibility of "irritation and inflammation of the reproductive tract" as a "plausibl[e]" "mechanism[]" of carcinogenesis.[92] The carcinogenesis of ovarian cancer is poorly understood overall, and the potential that chronic inflammation plays a role has been examined in a number of settings.[93] The studies that analyze whether the risk of ovarian cancer is increased in women with a history of pelvic inflammatory disease ("PID") are inconsistent.[94]

In addition, there are inconsistent data – as Dr. Wolf admits[95] – suggesting a possible protective effect of chronic non-steroidal anti-inflammatory drug ("NSAID") use against the future development of ovarian cancer. For example, Bonovas *et al.* is a meta-analysis that showed anti-

[87] Gertig D.M., Hunter D.J., Cramer D.W. *et al.* Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst* 2000; 92(3): 249-252.

[88] Terry K.L. *et al.* Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev Res* 2013; 6(8): 811-821; *see also* Cramer D.W. *et al.* The association between talc use and ovarian cancer. *Epidemiology* 2016; 27(3): 334-346 (Table 2) (reporting a higher OR for those with a history of hysterectomy or tubal ligation compared to patent women); Davis C.P. *et al.* Genital powder use and risk of epithelial ovarian cancer in the Ovarian Cancer in Women of African Ancestry Consortium. *Cancer Epidemiol Biomarkers Prev* 2021; 30: 1660-1668 (reporting a lower OR for patent women as compared to all women).

[89] Cramer D.W. *et al.* Ovarian cancer and talc: a case-control study. *Cancer* 1982: 50(2): 372-376 (Table 2 shows diaphragm use association was not statistically significant).

[90] Rosenblatt K.A. *et al.* Mineral fiber exposure and the development of ovarian cancer. *Gyn Onc* 1992; 45: 20-25 (Table 3 shows condom use association was not statistically significant: OR 1.6 (CI 0.6-3.9)); Cramer D.W. *et al.* Ovarian cancer and talc: a case-control study. *Cancer* 1982: 50(2): 372-376 (Table 2 shows condom use association was not statistically significant: adjusted RR 0.77 (0.41-1.44)).

[91] Wolf MDL Report at 14-16; Wolf 4/25/24 Dep. 17:13-18.

[92] O'Brien K.M. *et al.* Intimate care products and incidence of hormone-related cancers: a quantitative bias analysis. *Journal of Clinical Oncology* 2024; epub. ahead of print.

[93] Merritt M.A. *et al.* Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int J Cancer* 2008; 122(1): 170-176 ("These results in combination with previous studies suggest that chronic inflammation is unlikely to play a major role in the development of ovarian cancer.").

[94] Zhou Z. *et al.* Pelvic inflammatory disease and the risk of ovarian cancer: a meta-analysis. *Cancer Causes Control* 2017; 28(5): 415-428; Rasmussen C.B. *et al.* Is pelvic inflammatory disease a risk factor for ovarian cancer? *Cancer Epidemiol Biomarkers Prev* 2017; 26(1): 104-109; Stewart L.M. *et al.* Association between pelvic inflammatory disease, infertility, ectopic pregnancy and the development of ovarian serous borderline tumor, mucinous borderline tumor and low-grade serous carcinoma. *Gynecologic Oncology* 2020; 156(3): 611-615.

[95] Wolf MDL Report at 15.

inflammatory drug use did not reduce ovarian cancer risk.[96] Ni *et al.*, a pooled analysis of 13 case-control studies, one clinical trial and three cohort studies, also found no evidence of an association between aspirin use and ovarian cancer and did not find strong evidence of an association between non-aspirin NSAID use and ovarian cancer.[97] On the other hand, Trabert *et al*. did report a modest risk reduction for aspirin use but found no risk reduction for NSAID use.[98] The authors conducted another study in 2019 and also reported a modest decrease in risk reduction for aspirin use, but no risk reduction for other types of anti-inflammatories.[99] More recently, results from the PLCO Cancer Screening Trial revealed no "significant associations between aspirin use and ovarian cancer risk overall."[100] In clinical practice, NSAIDs are not recommended as a means to reduce the risk of ovarian cancer (unlike oral contraceptives).

There is no doubt that talc can induce a local inflammatory response in sufficient doses. In fact, this inflammatory response has been recognized for decades and led to one of the most common medical indications for talc: pleurodesis. Pleurodesis involves the direct injection of .5 to 10 grams of talc directly into the cavity surrounding the lungs (pleural cavity) in hopes of stimulating a strong inflammatory reaction that would cause scarring of the lung to the pleura and obliteration of potential space for air (pneumothorax) or fluid (pleural effusion). The procedure has been practiced since the 1930s.[101] It is important to recognize the biological similarities between the pleura and the peritoneum (the membrane lining the pelvic cavity that contains the fallopian tubes and ovaries). Both tissues are composed of mesothelial cells, both membranes protect internal organs and produce small amounts of lubricating fluid, and both can potentially undergo malignant transformation in the presence of carcinogens. Chronic asbestos exposure causes both pleural and peritoneal malignant mesothelioma, its hallmark cancers. Pleurodesis, therefore, offers years of clinical experience with which to examine the malignant potential of talc on mesothelial cells, cells that are very similar to those accepted as the origin of epithelial ovarian cancer. In 1979, a report was issued by the Research Committee of the British Thoracic Association on the long-term effects of pleurodesis using talc and kaolin in a group of patients with follow-up from 14 to 40 years.[102] Among 210 patients who underwent the procedure, there were three cases of lung cancer that developed in the cohort (not statistically

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[96] Bonovas S. *et al*. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. *Br J Clin Pharmacol* 2005; 60(2): 194-203.

[97] Ni X. *et al*. Meta-analysis on the association between non-steroidal anti-inflammatory drug use and ovarian cancer. *Br J Clin Pharmacol* 2012; 75(1): 26-35.

[98] Trabert B. *et al*. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the ovarian cancer association consortium. *J Natl Cancer Inst* 2014; 106(2): 1-11.

[99] Trabert B. *et al.* Analgesic use and ovarian cancer risk: an analysis in the ovarian cancer cohort consortium. *J Natl Cancer Inst* 2019; 111(2): 137-145.

[100] Hurwitz L.M. *et al.* Aspirin use and ovarian cancer risk using extended follow-up of the PLCO Cancer Screening Trial. *Gynecol Oncol* 2020; 159(2): 522-526; Hurwitz L.M. *et al.* Associations between daily aspirin use and cancer risk across strata of major cancer risk factors in two large U.S. cohorts. *Cancer Causes & Control* 2021; 32(1): 57-65.

[101] IARC Monograph. Carbon Black, Titanium Dioxide, and Talc, Volume 93. 2010; 93: 1-413, pg. 378.

[102] Research Committee of the British Thoracic Association and the Medical Research Council Pneumoconioisis Unit. A survey of the long-term effects of talc and kaolin pleurodesis. *Br J Dis Chest* 1979; 73: 285-288.

increased above expected). Two of these cancers occurred on the opposite side of the chest than the talc pleurodesis and no patient developed malignant mesothelioma.[103] Another study of 99 Danish patients who underwent pleurodesis between 1954 and 1964 and were followed for at least 20 years was published by Viskum *et al*.[104] Three cases of lung cancer occurred over the period of follow-up with one occurring in the contralateral lung not exposed to talc. Again, no cases of malignant mesothelioma occurred. Additionally, Györik *et al.* conducted a follow-up study in 63 patients with primary spontaneous pneumothorax who underwent talc pleurodesis.[105] One case of bronchogenic carcinoma was noted in a smoker, but no cases of malignant mesothelioma occurred. Talc remains the most commonly used sclerosing agent for pleurodesis worldwide.[106] Rather than data suggesting talc causes cancer of the pleura, a randomized controlled trial suggested it actually induces cancer cell death in patients with mesothelioma, leading to improved survival.[107]

Evaluating Causation

In 1965, Austin Bradford Hill[108] described the nine criteria that should be met to determine whether there is a causal relationship between an exposure and a disease. The nine "Bradford Hill" criteria are strength of association, consistency, temporality, dose-response, biologic plausibility, coherency, specificity, experimental evidence, and analogy.

The strength of association, which is determined by the risk estimates found in longitudinal and cross-sectional studies, is the first criterion. The higher the risk-estimate, the higher the likelihood that a causal relationship between the exposure and the disease exists. The lower the risk estimate, the higher the likelihood that the association is due to a confounding variable and that the association is spurious. Risk estimates (relative risks for case-control studies and hazard or odds ratios for prospective studies) are then further scrutinized to determine the range for which there is 95% certainty that the true risk estimate lies. This is called a 95% confidence interval (CI) and if the range crosses 1, the finding is not considered statistically significant regardless of whether the risk appears to be increased or decreased by a particular exposure.

Dr. Wolf emphasizes the significance of the slight increased risks found in the case-control studies that have found any increased risk at all, concluding that a 30-40% increase in risk (RR

[103] IARC Monograph. Carbon Black, Titanium Dioxide, and Talc, Volume 93. 2010; 93: 1-413, pg. 379.

[104] Viskum K. *et al*. Long term sequelae after talc pleurodesis for spontaneous pneumothorax. *Pneumologie* 1989; 43: 105-106.

[105] Györik S. *et al.* Long-term follow-up of thoracoscopic talc pleurodesis for primary spontaneous pneumothorax. *Eur Respir J* 2007; 29(4): 757-760.

[106] Korsic M. *et al*. Talc pleurodesis improves survival of patients with malignant pleural effusions: case-control study. *Wien Klin Wochenschr (Central Eur J Med)* 2015; 127: 963-969.

[107] Davies H.E. *et al*. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA* 2012; 307(22): 2383-2389; Nasreen N. *et al.* Talc induces apoptosis in human malignant mesothelioma cells in vitro. *Am J Respir Crit Care Med* 2000; 161: 595-600.

[108] Hill A.B. The environment and disease: association or causation? *Proc Royal Soc Med* 1965; 58: 295-300.

1.3-1.4) satisfies the strength-of-association consideration.[109] But an increased risk of this level is generally considered to be either a weak association or no association at all;[110] in fact, Hill used examples where the increased risk was ten-fold and even greater in illustrating this factor.[111] By way of comparison, risk estimates for ovarian cancer associated with talc use from case-control studies show less than a two-fold increased risk, while the estimates of the relative risk of lung cancer in the long-term smokers compared with the lifetime nonsmoker vary from 10- to 30-fold. Comparatively, the presence of Human Papilloma Virus is associated with a 50-100-fold increased risk of cervical cancer.[112] The case-control studies involving talc therefore fail to satisfy the strength-of-association criterion.

Consistency of results among various studies of different types and in different populations is also a very important consideration. As set forth above in my discussion of the epidemiological studies, the results of the studies are inconsistent. In particular, approximately half of the case-control studies and all of the cohort studies found no significant increased risk of EOC from genital talc use.[113] Thus, Dr. Wolf is wrong to suggest that "[t]he magnitude of risk has been consistent over four decades [and] across various geographic populations."[114] In addition, as demonstrated in the Schildkraut publication, the litigation publicity post-2014 may have affected

[109] Wolf MDL Report at 17-18.

[110] Wentzensen N. & O'Brien K.M. Talc, body powder, and ovarian cancer: a summary of the epidemiologic evidence. *Gynecologic Oncology*. 2021; 163(1): 199-208 ("Given the rarity of ovarian cancer in the general population, the small increase in relative risk translates to a very low increase in absolute risk. Further research is needed to understand the underpinnings of the observed association between genital powder use and ovarian cancer risk.").

[111] Hill A.B. The environment and disease: association or causation? *Proc Royal Soc Med* 1965; 58: 295-300.

[112] Bosch F.X. *et al*. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 2002; 55(4): 244-265.

[113] Goodman J.E. *et al.* A critical review of talc and ovarian cancer. *J of Toxicology and Environmental Health, Part B* 2020; 23(5): 188-213 ("The hypothesis that talc exposure induces ovarian cancer is only supported if one discounts the null results of the cohort studies . . . . It is concluded that the evidence does not support a causal association between perineal talc use and ovarian cancer.").

[114] Wolf MDL Report at 18; Wolf MDL Report at 7 (citing Wu 2015, Cramer 2016, and Schildkraut 2016).

the ORs due to the potential for recall bias. Talc exposure was similar in both cases and controls prior to 2014, and diverge only after that year.[115]

Table 2. Adjusted ORs for the associations between mode, frequency, and duration of body powder use and ovarian cancer in the AACES

Exposure	Cases (n = 584) n (%)	Controls (n = 745) n (%)	OR[a] (95% CI)
Body powder use			
Never use	217 (37.2)	351 (47.1)	1.00 (Referent)
Ever use	367 (62.8)	394 (52.9)	1.39 (1.10–1.76)
Body powder use by location			
Never use	217 (37.2)	351 (47.1)	1.00 (Referent)
Only nongenital use	119 (20.4)	140 (18.8)	1.31 (0.95–1.79)
Any genital use	248 (42.5)	254 (34.1)	1.44 (1.11–1.86)
Interview date <2014	(n = 351)	(n = 571)	
Never use	147 (41.9)	286 (48.4)	1.00 (Referent)
Only nongenital use	76 (21.7)	104 (17.6)	1.40 (0.96–2.03
Any genital use	128 (36.5)	201 (34.0)	1.19 (0.87–1.63)
Interview date >2014	(n = 233)	(n = 154)	
Never use	70 (30.0)	65 (42.2)	1.00 (Referent)
Only nongenital use	43 (18.4)	36 (23.3)	1.26 (0.69–2.32
Any genital use	120 (51.5)	53 (34.4)	2.91 (1.70–4.97
Frequency of use			
Never use	217 (37.3)	351 (47.2)	1.00 (Referent)
Only nongenital use			
Less than daily	61 (10.5)	82 (11.0)	1.15 (0.78–1.71)
Daily	58 (10.0)	58 (7.8)	1.53 (1.00–2.35
P_{trend}			0.09
Any genital use			
Less than daily	88 (15.1)	119 (16.0)	1.12 (0.80–1.58)
Daily	158 (27.2)	134 (18.0)	1.71 (1.26–2.33)
P_{trend}			<0.01
Duration of use			
Never use	217 (37.4)	351 (47.4)	1.00 (Referent)
Only nongenital use			
<20 years	59 (10.2)	68 (9.2)	1.37 (0.91–2.07
>20 years	60 (10.3)	70 (9.5)	1.28 (0.85–1.93
P_{trend}			0.13
Any genital use			
<20 years	101 (17.4)	118 (15.9)	1.33 (0.95–1.86
>20 years	144 (24.8)	134 (18.1)	1.52 (1.11–2.07)
P_{trend}			0.02
Lifetime body powder applications			
Never use	217 (37.4)	351 (47.4)	1.00 (Referent)
Only nongenital use			
Below median (<3,600 applications)	60 (10.3)	72 (9.7)	1.35 (0.90–2.0
Above median (>3,600 applications)	59 (10.2)	66 (8.9)	1.30 (0.86–1.97
P_{trend}			0.14
Any genital use			
Below median (<3,600 applications)	92 (15.9)	119 (16.1)	1.16 (0.83–1.63
Above median (>3,600 applications)	152 (26.2)	133 (17.9)	1.67 (1.23–2.26
P_{trend}			<0.01

[a]Adjusted for age at diagnosis/interview, study site, education, tubal ligatic parity, BMI, duration of OC use, first-degree family history of breast or ovari cancer, and interview year.

The studies also fail to show a consistent dose-response relationship, whereby increasing levels of exposure are associated with increased risk of ovarian cancer. Dr. Wolf cites to the 2016 Cramer study in asserting that risk of EOC increases with frequency and duration of use.[116] Cramer reported an increased risk of EOC based on total lifetime applications of talc, finding that there was a statistically significant risk from 1-5 years of daily use (RR 1.38, 95% confidence interval 1.01-1.88), and after the equivalent of more than 20 years of daily use (RR 1.49, 95% confidence interval 1.06-2.10). However, women who reportedly used talcum powder for the equivalent of between 5-20 years did not have a statistically significant increased risk (RR 1.16, 95% confidence interval .80-1.66). Dr. Wolf also points to the Schildkraut study as support for the same point that risk increases with duration and frequency of talc use.[117] The Schildkraut study, however, only reported the difference in risk between women who had used talc for less than 20 years and 3,600 applications and more than 20 years and 3,600 applications.[118] Demonstrating a trend in dose-response is not possible given that there were only two data points. Moreover, there have been several case-control studies that reported no dose-response relationship, including Davis (2021), which included some of the same co-authors.[119] For example, Cook *et al.* assessed cumulative lifetime days for various types of exposure, including perineal dusting.[120] There

[115] Schildkraut J.M. *et al.* Association between body powder use and ovarian cancer: the African American cancer epidemiology study (AACES). *Cancer Epidemiol Biomarkers Prev* 2016; 25(10): 1411-1417 (Table 2).

[116] Wolf MDL Report at 7.

[117] Wolf MDL Report at 7.

[118] Schildkraut J.M. *et al.* Association between body powder use and ovarian cancer: the African American cancer epidemiology study (AACES). *Cancer Epidemiol Biomarkers Prev* 2016; 25(10): 1411-1417.

[119] Davis C.P. *et al.* Genital powder use and risk of epithelial ovarian cancer in the Ovarian Cancer in Women of African Ancestry Consortium. *Cancer Epidemiol Biomarkers Prev* 2021; 30: 1660-1668.

[120] Cook L.S. *et al.* Perineal powder exposure and the risk of ovarian cancer. *Am J Epidemiol* 1997; 145(5): 459-465.

was no statistically significant elevated risk for any of the types of exposure examined. The relative risk for the group with fewer than 2,000 cumulative days of use (RR 1.8, 95% confidence interval 0.9-3.5) reported essentially matching risk estimates as the group with greater than 10,000 cumulative days of use (RR 1.8, 95% confidence interval 0.9-3.4). Mills *et al.* examined frequency and duration of use by quartiles, reporting risks of 1.03, 1.81, 1.74 and 1.06 for ascending quartiles.[121] The authors concluded that a dose-response association was not found. And Rosenblatt *et al.* examined the association across four categories of increasing lifetime applications.[122] There was no statistically significant elevated risk for women who reported between 4,800 and 9,999 lifetime applications (RR 0.78, 95% confidence interval 0.41-1.48 for invasive tumors; RR 0.87, 95% confidence interval 0.5-1.53 for all tumors) and women with more than 10,000 lifetime applications (RR 0.84, 95% confidence interval 0.44-1.59 for invasive tumors; RR 0.87, 95% confidence interval 0.48-1.57 for all tumors).

Plaintiffs have also failed to put forward any accepted biological mechanism by which genital talc use could cause EOC. Reliance on studies showing migration of "motile" sperm and bacteria[123] is misplaced because the movement of these substances is obviously and starkly different from any purported mobility of talc. Additionally, although Dr. Wolf points to studies that identified talc particles in ovarian tissue, this fact cannot be evidence of talc migration because, as mentioned, those studies have found talc particles in the ovaries of women with and without perineal talc use. For example, the Heller (1996) study cited by Dr. Wolf[124] found that "talc particles were observed to a similar extent with both exposed and unexposed subjects."[125]

Dr. Wolf points to work done by plaintiffs' expert Dr. Ghassan Saed (including articles on which Nicole Fletcher or Amy Harper are listed as the first author) in support of her contention that experimentation confirms that talc use causes ovarian cancer.[126] My understanding is that Dr. Saed's manuscript claiming to provide evidence that talc causes malignant transformation of human ovarian cells has been rejected as unreliable and fundamentally unsupported by multiple journals that have evaluated his studies.[127] Regardless, none of Dr. Saed's *in vitro* results have been replicated in any *in vivo* studies.[128] In addition, although Dr. Wolf contends that

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[121] Mills P.K. *et al.* Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *Int J Cancer* 2004; 112: 458-464.

[122] Rosenblatt K.A. *et al.* Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes Control* 2011; 11: 737-742.

[123] Wolf MDL Report at 12-13.

[124] Wolf MDL Report at 13.

[125] Heller D.S. *et al.* The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Am J Obstet Gynecol* 1996; 174: 1507-1510.

[126] Wolf MDL Report at 15.

[127] *See* SAED_SEPT222021_SUPPL_000005; SAED_SEPT222021_SUPPL_000042; SAED_SEPT222021_SUPPL_000069-70; SAED_SEPT222021_SUPPL_000100-104; SAED_SEPT222021_SUPPL_000128.

[128] The same is true for other studies that Dr. Wolf claims are "consistent" with Dr. Saed's results. For instance, Mandarino A. *et al.* The effect of talc particles on phagocytes in co-culture with ovarian cancer cells. *Environmental Research* 2020; 180: 108676, which Dr. Wolf also relies on, Wolf MDL Report at 15. Mandarino *et al.* examined the effect of talc on phagocytic cells and concluded that their "findings suggest that in vitro exposure to talc,

inflammation is the mechanism by which talc can cause cancer, an inflammatory response is not the equivalent of malignant transformation. As described above, talc is used in pleurodesis, which causes inflammation, but has not been identified as increasing cancer risk. In fact, recent studies suggest an improved survival rate in patients with pleural mesothelioma treated with talc pleurodesis.[129] Moreover, the expected inflammatory reaction (foreign body granulomas) has not been identified in tissue of women with ovarian cancer, even in the presence of talc.[130]

Another Bradford Hill factor is analogy – i.e., whether there are similar associations that have been confirmed as causal. Dr. Wolf points to "other diseases caused by various and specific carcinogens"[131] and provides the following examples: "smoking causes lung cancer, asbestos causes mesothelioma and ovarian cancer, sun exposure causes skin cancer, and HPV causes cervical cancer."[132] She goes on to incorrectly assert that "[a]ll of these cancers are the result of an inflammatory process initiated by a foreign agent."[133] HPV does not cause cervical cancer via inflammation, but rather by molecular interactions between viral and host gene products. In fact, in the case of HPV, inflammation actually decreases the risk of persistent infection and progression of precursor lesions toward cancer.[134] More importantly, just because some environmental factors cause some types of cancer, that does not mean they are analogous to the proposed association between talc and ovarian cancer.

Conclusion

As a gynecologic oncologist, I have focused my entire career on the study and treatment of ovarian cancer and other gynecological diseases. I believe that it is essential that scientific resources are dedicated to understanding ovarian cancer and investigating potential causes of the disease. But it is just as important that those resources are not wasted on efforts to establish an association between ovarian cancer and talc exposure (or any other factor) based on a hypothesis that is being pursued in connection with product liability litigation. Indeed, such efforts distract

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particularly in a high-estrogen environment, may compromise immunosurveillance functions of macrophages." But the authors conceded that further research on the issue is required. Similarly, Emi T. et al. Transcriptomic and epigenomic effects of insoluble particles on J774 macrophages. *Epigenetics* 2021; 16(10): 1053-1070, purported to show changes in gene expression in macrophages exposed to talc *in vitro*. The study authors termed their findings a "hypothesis that merits future testing." Notably, *in vivo* studies have examined phagocytic cell function in rodents following talc exposure and found a persistent decrease in macrophage phagocytosis activity. Beck B.D. *et al.* The pulmonary toxicity of talc and granite dust as estimated from an in vivo hamster bioassay. *Toxicology and Applied Pharmacology* 1987; 87(2): 222-234.

[129] Korsic M. *et al*. Talc pleurodesis improves survival of patients with malignant pleural effusions: case-control study. *Wien Klin Wochenschr (Central Eur J Med)* 2015; 127: 963-969.

[130] Heller D.S. *et al*. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Am J Obstet Gynecol* 1996; 174: 1507-1510.

[131] Wolf MDL Report at 19.

[132] Wolf MDL Report at 19.

[133] Wolf MDL Report at 19.

[134] Kovacic M.B. *et al.* Epidemiologic analysis of histologic cervical inflammation: relationship to human papillomavirus. *Human Pathology* 2008; 39: 1088-1095.

the medical and scientific communities' attention from legitimate science-based areas of inquiry and research.

This diversion of the scientific community's attention is evident in the work of Penninkilampi and Eslick,[135] discussed above, who devoted significant time and resources to a meta-analysis evaluating ovarian cancer and genital talc use that was admittedly based, at least in part, on media and other attention spurred by this litigation – and then pointedly excluded qualifying studies from their analysis that failed to show such a link.

The gravity of ovarian cancer requires independent, patient-focused research and not litigation-driven research or multiple meta-analyses all examining the same flawed studies.

Ovarian cancer is the deadliest of all gynecologic cancers. There is no effective screen for early detection and our ability to reverse the chemo-resistance that ultimately leads to the death of our patients has been disappointing. Surely if convincing data existed regarding an easily eradicated cause of the disease, the gynecologic oncology community would aggressively pursue a public health agenda to do just that. No such effort exists for a reason. As a gynecologic oncologist, I urge my patients and my primary care colleagues to be aware of the symptoms of ovarian cancer, I educate my patients on the importance of genetic counseling and testing, and I continue to research innovations that could lead to earlier detection. I do not recommend against genital talc use because there is insufficient data to support such a recommendation.

As detailed below, these conclusions apply with equal force to my opinion that genital talcum powder use did not cause Anna Gallardo to develop ovarian cancer.

[135] Penninkilampi R. & Eslick G.D. Perineal talc use and ovarian cancer: a systematic review and meta-analysis. *Epidemiology* 2018; 29: 41-49.

Anna Gallardo Case-Specific Opinions
Kevin Holcomb MD

I have reviewed Ms. Gallardo's available medical records, the plaintiff profile sheet, and the depositions of Ms. Gallardo, her husband Ramon Gallardo, and Dr. David Mutch, one of Ms. Gallardo's treating physicians. My medical education, training, and clinical experience, which qualify me as an expert in ovarian cancer causes and treatment, are outlined separately in my general causation MDL report. I have considered the case-specific factors and the totality of the scientific data regarding talc as a potential cause of ovarian cancer to reach the conclusion that Ms. Gallardo's reported use of talcum powder did not contribute to her development of endometrioid ovarian cancer.

Medical History

Ms. Gallardo was born in September 1952. In May 2013, at the age of 60, she presented to her gynecologist, Dr. Gary Wasserman, for a well woman exam. She complained of post-menopausal vaginal bleeding "for several days."[136] An endometrial biopsy was performed revealing proliferative endometrium but no hyperplasia or malignancy.[137] Ms. Gallardo returned a week later for an ultrasound to address her bleeding. The ultrasound showed a normal right ovary and an enlarged left ovary.[138] On July 16, 2023, lab results revealed substantially elevated levels of ovarian tumor biomarker CA-125 at 217 (compared to normal levels in healthy women of ≤34).[139] Three days later, on July 19, Ms. Gallardo returned for an abdominal CT scan. The CT scan showed a 7.4 cm adnexal mass attached to the right pelvic side wall, thought to potentially represent ovarian carcinoma. It also revealed thickened endometrium and prominent soft tissue on the left.[140] The following week, Ms. Gallardo underwent a total hysterectomy and bilateral salpingo-oophorectomy (i.e., removal of the uterus and both ovaries and fallopian tubes). The surgery confirmed a large, partially-solid mass comprising the left ovary and fallopian tube. The right ovary and tube were grossly normal.[141] The final pathology report revealed endometrioid adenocarcinoma, with synchronous primary tumors on both the left and right ovaries. The left tumor was 8.5 cm, poorly differentiated without evidence of surface involvement, and FIGO Grade 3. The right ovary showed endometrioid adenocarcinoma present on the ovarian surface. There was no fallopian tube involvement. There was no evidence of uterine malignancy, or further metastasis. The cancer was staged IIA.[142]

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[136] GALLARDO_ANNA_DRWASSERMAN_00136-00158; GallardoA-MMTSLMR-00073-00084.

[137] GallardoA-MMTSLMR-00084-00085.

[138] GallardoA-MMTSLMR-00069.

[139] GALLARDO_ANNA_DRWASSERMAN_00247.

[140] GALLARDO_ANNA_DRWASSERMAN_00296.

[141] GALLARDO_ANNA_BJH_00011-00014.

[142] GALLARDO_ANNA_BJH_00001-00006.

As is standard practice, following surgery, Ms. Gallardo received six cycles of chemotherapy treatment with carboplatin and paclitaxel (trade-name Taxol). Chemotherapy was described as proceeding "remarkably well."[143] At a follow-up evaluation after the completion of chemotherapy, doctors found no evidence of disease and a "[n]ormal [g]yn[ecological] evaluation."[144] Ms. Gallardo has remained cancer-free for more than ten years since.

Ms. Gallardo had an extensive family history of cancer (including multiple myeloma, kidney cancer, and leukemia). As such, Ms. Gallardo was referred to genetic testing and counseling in January of 2014. Eleven genes associated with increased risk of breast, colon, and gynecological cancers were sequenced – BRCA1, BRCA2, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53.[145] The testing found "[n]o reportable variants" in these genes, but cautioned "negative result[s] do[] not exclude a genetic basis for reported personal and/or family history of cancer" because it remains "possible that this patient ha[d] a pathogenic mutation that was not detectable by this analysis or in a gene that [was] not included on panel."[146] The provider noted "a more comprehensive genetic panel may be considered as clinically indicated."[147] If Ms. Gallardo had been my patient, I would have recommended further comprehensive genetic testing and re-testing. My position is supported by the testimony of her treating physician, Dr. Mutch, who stated she was likely due for retesting in 2021.[148]

Exposure History.
Ms. Gallardo claims to have applied talcum powder to her genital area daily from 1968 to 1988.[149] She has not used any talc since then.[150]

Analysis.
After reviewing the available medical records, depositions, and plaintiff fact sheet, it is my opinion that Ms. Gallardo's reported use of talcum powder products did not contribute to her development of ovarian cancer. My opinion is reached to a reasonable degree of medical and scientific certainty. As my general causation report outlines, the totality of epidemiologic data evaluating genital talc use and the risk of subsequent ovarian cancer do not support an association, much less a causal relationship. The highest quality prospective cohort studies with long-term follow up have suggested no association between the two, and the lower-quality retrospective studies demonstrate a weak

[143] GALLARDO_ANNA_DRWASSERMAN_00210.

[144] GALLARDO_ANNA_DRMUTCH_00078-00079.

[145] GallardoA-WUSTLMR-00123-00124.

[146] GALLARDO_ANNA_DRMUTCH_00001-00004.

[147] GALLARDO_ANNA_DRMUTCH_00001-00004.

[148] Dep. of David G. Mutch, M.D. ("Mutch Dep.") 53:17-21, 55:1-10, Feb. 13, 2021.

[149] Gallardo Plaintiff Profile Form at 16.

[150] Dep. of Anna Gallardo ("Gallardo Dep.") 38:6-13, Jan. 12, 2021.

association in only approximately 50% of the studies. The data with respect to endometrioid cancer specifically are similar to the data with respect to ovarian cancer generally, although some studies suggest an even weaker association for endometrioid cancer.[151]

Even if talcum powder could theoretically cause endometrioid cancer in some circumstances, there is nothing to suggest that it caused Ms. Gallardo's cancer. Importantly, even if talcum powder genuinely elevated the risk of ovarian cancer by the magnitude suggested in certain case-control studies, that would not mean any given case of ovarian cancer (even in a woman who used talcum powder) could be attributed to talc. For instance, given an odds ratio of 1.5 (near the upper end of those reported in the case-control literature), 67% of cases in exposed women would still be attributed to background risk rather than to the exposure. It is also critical to understand that a portion of endometrioid cancers arise idiopathically – that is, they cannot be attributed to any environmental factor or identifiable genetic factor. Like all cancers, these involve the dysfunction of genes that ordinarily prevent the out-of-control cell division that leads to tumors, but the underlying cause of those genetic changes cannot be identified.

Ms. Gallardo's reproductive history is generally not associated with substantial increases or decreases in ovarian cancer risk:

- Parity. Multiparity[152] is generally associated with a decreased risk of ovarian cancer, while nulliparity is generally associated with increased risk. Ms. Gallardo had one child.[153]
- Hormonal birth control. Use of hormonal birth control for five or more years is generally associated with a decreased risk of ovarian cancer.[154] Ms. Gallardo did use hormonal birth control, but only for three years.
- Breastfeeding. Breastfeeding for longer than a year has been associated in some studies with a moderate reduction in ovarian cancer risk.[155] Ms. Gallardo breastfed her child for just six weeks.
- Post-menopausal hormone replacement therapy. Ms. Gallardo's records report post-menopausal hormone replacement therapy. Hormone therapy is associated

[151] *E.g.*, Cramer D.W. *et al.* Genital talc exposure and risk of ovarian cancer. *Int J Cancer* 1999; 81: 351-356.

[152] *E.g.*, Gaitskell K. *et al.* Histological subtypes of ovarian cancer associated with parity and breastfeeding in the prospective Million Women Study. *Int J Cancer* 2018; 142: 281-289.

[153] Gallardo Plaintiff Profile Form at 17.

[154] *E.g.*, IARC Monograph. Pharmaceuticals, Combined Estrogen-Progestogen Contraceptives, Volume 100A. 2012; 100(A): 283-311; Havrilesky L.J. *et al.* Oral contraceptive pills as primary prevention for ovarian cancer. *Obstetrics & Gynecology* 2013; 122(1): 139-147; Wentzensen N. *et al.* Ovarian cancer risk factors by histologic subtype: An analysis from the Ovarian Cancer Cohort Consortium. *Journal of Clinical Oncology* 2016; 34(24): 2888-2898.

[155] *E.g.*, Gaitskell K. *et al.* Histological subtypes of ovarian cancer associated with parity and breastfeeding in the prospective Million Women Study. *Int J Cancer* 2018; 142: 281-289.

with an increased risk for ovarian cancer overall and endometrioid cancers in particular.[156]

- Menarche and menopause. Early menarche and late menopause (i.e., a longer total ovulatory period) are both associated with increased risk of ovarian cancer. Ms. Gallardo had her first menstrual period at 12 and menopause sometime around 51.[157] Both are nearly exactly average.

Previous/Preexisting Conditions. Ms. Gallardo's records report some history of gynecological conditions, including fibroid uterus, a benign cervical polyp, and a benign labial lipoma. These conditions do not meaningfully contribute to the risk of endometrioid ovarian cancer. Ms. Gallardo's medical history is negative for endometriosis, even though ovarian endometrioid cancer usually arises from endometriosis.[158] Ms. Gallardo's surgeon did note endosalpingiosis in the posterior cul de sac peritoneum,[159] which has been associated with ovarian cancer.[160] In addition, Ms. Gallardo reported having used hormone replacement therapy during menopause.[161] As has been discussed, hormone replacement therapy is a potential risk factor for ovarian cancer.

Age. All types of epithelial ovarian cancer, including endometrioid cancer, are typically diagnosed in post-menopausal women with an average age at diagnosis of 62 years. Ms. Gallardo was diagnosed post-menopause, but at a slightly earlier-than-average age, 60 years. Early onset of disease is a characteristic of epithelial ovarian cancers associated with hereditary predisposition syndromes, something that is possible in light of her family history.

Family History. Ms. Gallardo has an extensive family history of cancer, which increases risk of any cancer, including endometrioid ovarian cancer. With that said, she did not report family history of breast, colon, or ovarian cancer, which are the most strongly linked to the risk of ovarian cancer. In particular, Ms. Gallardo's father had multiple myeloma. Three second-degree relatives had cancer: an uncle with kidney cancer, and an aunt and half-brother had leukemia. As mentioned, this extensive family history prompted Ms. Gallardo's doctors to recommend genetic testing "regarding [the] potential for

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[156] *E.g.*, Liu Y. Menopausal hormone replacement therapy and the risk of ovarian cancer: a meta-analysis. *Front Endocrinol* 2019; 10: 801.

[157] Medical records report menopause in 2004, when Ms. Gallardo would have been 51 or 51. GALLARDO_ANNA_DRWASSERMAN_00016.

[158] McConechy M.K. *et al.* Ovarian & endometrial endometrioid carcinomas have distinct CTNNB1 and PTEN mutation profiles. *Modern Pathology* 2024; 27: 128-134.

[159] Mutch Dep. 23:23-25.

[160] Hermens M. *et al.* Increased association of ovarian cancer in women with histological proven endosalpingiosis. *Cancer Epidemiol* 2020; 65: 101700 found an incidence rate ratio of 38.8 (95% CI 29.3-50.4), even when cases with concurrent endometriosis were excluded.

[161] Gallardo Dep. 50:13-51:1.

hereditary disease."[162] This family history is concerning for inherited risk, which, as discussed below, and genetic testing did not rule out.[163]

Genetic Risk. Ms. Gallardo was tested on a panel of 11 genes that contribute to increased risk of breast, colon, and ovarian cancers as part of GeneDx's endometrial cancer panel and was found to have no deleterious mutations. This does not rule out a hereditary cause of her ovarian cancer – a fact noted by her genetic testing report. Advances in our understanding of the genetic causes of ovarian cancer have identified novel mechanisms in loss of function of BRCA, as well as a number of additional genetic alterations that significantly increase a woman's risk for the disease.[164] For example, large site rearrangements in the BRCA genes can render these tumor-suppressor genes inactive and are not detected by the traditional sequencing methods in use at the time of her testing in 2014. These clinically significant changes can be detected by an additional test called "BART," which was available in 2014 but does not appear to have been conducted. A number of genes involved in DNA mismatch repair and the DNA homologous recombination repair pathway can harbor inherited mutations that significantly increase a woman's risk of ovarian cancer. These include RAD51, BRIP1, and PALB2. Ms. Gallardo has yet to be tested for any of these genetic mutations, which are standard components of current ovarian cancer predisposition testing.

Environmental factors. There are few environmental factors thought to be associated with ovarian cancer risk. Ms. Gallardo reports no history of cigarette smoking, an environmental factor associated only with mucinous adenocarcinoma of the ovary. Both her parents and husband smoked, however. She has no history of heavy occupational asbestos exposure. She is not obese.

In many, if not most, cases of ovarian cancer, the cause of any individual ovarian cancer cannot be specifically identified. Ms. Gallardo's case appears to be one such example. I have reviewed the report of Dr. Judith Wolf, in which she purports to have performed a differential diagnosis and concluded that talcum powder caused Ms. Gallardo's ovarian cancer. Dr. Wolf's report suffers from several logical fallacies, the most severe of which is the belief that all cancer must have an identifiable cause. Dr. Wolf appears to reason that because Ms. Gallardo used talcum powder and had few identifiable genetic or environmental risk factors, the talcum powder must be to blame. This is not consistent with sound medical or scientific practice. As I mentioned earlier, even if talcum powder genuinely increased the risk of ovarian cancer, most cases, even among exposed women, would be attributable to the background risk instead.

[162] GALLARDO_ANNA_DRMUTCH_00077-00078.

[163] 4/25/24 Wolf Dep. 31:8:18 (noting that "some type of inherited gene mutation" "could be one reason" for an individual's increased risk of cancer due to familial history of cancer).

[164] Dr. Wolf acknowledged at her deposition that Ms. Gallardo was not tested for certain gene mutations that have been associated with ovarian cancer. 4/25/24 Wolf Dep. 34:24-35:24; *id.* 37:12-18.

My conclusions are consistent with those reached by independent medical professionals. No physician or allied health professional involved in the excellent care Ms. Gallardo received inquired about or recommended against her use of talcum powder. In fact, her treating physician, Dr. Mutch, agrees with my assessment that the epidemiological evidence does not support a causal relationship between talcum powder and endometrioid ovarian cancer.[165]

After receiving ovarian cancer treatment from some of the finest medical institutions and physicians in the United States (none of whom appear to believe that talc caused her cancer), Ms. Gallardo first learned of the purported association between ovarian cancer and talcum powder use from a television news story about a different lawsuit. In my opinion, such advertising does a disservice to women like Ms. Gallardo by misleading them about their health.

[165] *See* Mutch Dep. 60:4-61:19.

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Other materials reviewed:

- November 16, 2018 Expert Report of Judith Wolf, MD, *In re Johnson & Johnson Talcum Powder Products Marketing, Sales Practices, and Products Liability Litigation*, MDL No. 16-2738 (D.N.J.).

- July 2, 2021 Amended Expert Report of Judith Wolf, MD, *In re Johnson & Johnson Talcum Powder Products Marketing, Sales Practices, and Products Liability Litigation*, MDL No. 16-2738 (D.N.J.).

- November 15, 2023 Second Amended Expert Report of Judith Wolf, MD, *In re Johnson & Johnson Talcum Powder Products Marketing, Sales Practices, and Products Liability Litigation*, MDL No. 16-2738 (D.N.J.).

- July 2, 2021 Expert Report of Judith Wolf, MD, *Gallardo v. Johnson & Johnson*, No. 3:18-cv-10840 (D.N.J.).

- November 15, 2023 Amended Expert Report of Judith Wolf, MD, *Gallardo v. Johnson & Johnson*, No. 3:18-cv-10840 (D.N.J.).

- January 7, 2019 Deposition transcript of Judith K. Wolf, M.D. and exhibits.

- September 13, 2021 Deposition transcript of Judith K. Wolf, M.D. and exhibits.

- September 14, 2021 Deposition transcript of Judith K. Wolf, M.D. and exhibits.

- January 10, 2024 Deposition transcript of Judith K. Wolf, M.D. and exhibits.

- April 25, 2024 Deposition transcript of Judith K. Wolf, M.D. and exhibits.
- January 23, 2019 Deposition transcript of Ghassan Saed, Ph.D. and exhibits.
- February 14, 2019 Deposition transcript of Ghassan Saed, Ph.D. and exhibits.
- February 13, 2021 Deposition transcript of David G. Mutch, M.D.
- January 12, 2021 Deposition transcript of Anna Gallardo and exhibits.
- Anna Gallardo Medical Records.
- Anna Gallardo Plaintiff Profile Form.
- SAED_SEPT222021_SUPPL_000001 - SAED_SEPT222021_SUPPL_000284.

Table 1

Study Type	Year	Author	Journal	Title	Analysis	Odds Ratio / Relative Risk	95% CI
Case-Control	1982	Cramer	Cancer	Ovarian cancer and talc: A case-control study	Any perineal exposure (via dusting and/or napkins)	1.92	(1.27, 2.89)
Case-Control	1983	Hartge	JAMA	Talc and ovarian cancer	Any talc use; Any genital talc use (on genitals, napkins, or underwear)	0.7 (Any talc); 2.5 (Genital)	(0.40, 1.10) Any talc; (0.70, 10.0) Genital
Case-Control	1988	Whittemoore	Am J Epidemiol	Personal and environmental characteristics related to epithelial ovarian cancer. Exposures to talcum powder, tobacco, alcohol, and coffee	"Perineum only" talc use	1.45	(0.81, 2.60)
Case-Control	1989	Booth	BR Cancer	Risk factors for ovarian cancer: A case-control study	Daily talc use in genital area	1.3	(0.80, 1.9)
Case-Control	1989	Harlow	Am J Epidemiol	A case-control study of borderline ovarian tumors: The influence of perineal exposure to talc	Any perineal exposure to powder	1.1	(0.70, 2.1)
Case-Control	1992	Chen	Int J Epidemiol	Risk factors for epithelial ovarian cancer in Beijing, China	≥3 months of application of talc-containing dusting powder to the lower abdomen and perineum	3.9	(0.9, 10.6)
Case-Control	1992	Harlow	Obstet Gynecol	Perineal exposure to talc and ovarian cancer risk	Any genital talc application	1.5	(1.0, 2.1)
Case-Control	1992	Rosenblatt	Gynecol Oncol	Mineral fiber exposure and the development of ovarian cancer	Genital bath talc use (Yes/No)	1.7	(0.70, 3.9)
Case-Control	1993	Tzonou	Int J Cancer	Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer	"Talc application in the perineum"	1.05	(0.28, 3.98)
Case-Control	1995	Cramer	AEP	Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer	Talc use (Yes/No)	1.6	(1.2, 2.1)
Case-Control	1995	Purdie	Int J Cancer	Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study	Use of talc around abdomen/perineum	1.27	(1.04, 1.54)
Case-Control	1997	Chang	Cancer	Perineal talc exposure and risk of ovarian carcinoma	"Any regular talc exposure"	1.42	(1.08, 1.86)
Case-Control	1997	Cook	Am J Epidemiol	Perineal powder exposure and the risk of ovarian cancer	Any use of talcum powder	1.6	(0.9, 2.8)
Case-Control	1997	Green	In J Cancer	Tubal sterilization, hysterectomy and decreased risk of ovarian cancer.	"Use of talc in the perineal region" among women with surgical tubal occlusion; Among women without surgical sterilization	1.3 (With surgery); 1.3 (Without)	(1.1, 1.6) With surgery; (1.0, 1.7) Without
Case-Control	1998	Godard	Am J Obstet Gynecol	Risk factors for familial and sporadic ovarian cancer among French Canadians: A case-control study	Ever/never "Use of talc on perineum"	2.49	(0.94, 6.58)
Case-Control	1999	Cramer	International J of Cancer	Genital talc exposure and risk of ovarian cancer	Any personal genital powder exposure	1.6	(1.18, 2.15)
Case-Control	1999	Wong	Obstet Gynecol	Perineal talc exposure and subsequent epithelial ovarian cancer: A case-control study	Talc use on genital/thigh area and on sanitary napkins	1.1	(0.7, 1.7)
Case-Control	2000	Ness	Epidemiol	Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer	Genital/rectal use (at least once per month for six or more months)	1.5	(1.1, 2.0)
Case-Control	2004	Mills	Am J Epidemiol	Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California	Ever/never genital talc use	1.37	(1.02, 1.85)
Case-Control	2004	Pike	Fertil Steril	Hormonal factors and the risk of invasive ovarian cancer: A population based case control study	"Use of genital area talc" (Yes/No)	1.6	(1.18, 2.18)
Case-Control	2005	Cramer	Cancer Epid Bio Prev	Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer	"Genital use" of talc	1.16	(0.9, 1.49)
Case-Control	2007	Jordan	Obstet Gynecol	Risk factors for benign serous and mucinous epithelial ovarian tumors	"Use of talc in the Perineal Region" (Yes/No)	1.1	(0.84, 1.45)
Case-Control	2008	Gates	Cancer Epid Bio Prev	Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer	"Regular genital talc use" (once per week or more)	1.36	(1.14, 1.63)
Case-Control	2008	Goodman	Endcor Relat Cancer	Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk	Genital powder use (*As reported in Terry 2013 pooled analysis, ref. 25)	0.99	(0.70, 1.41)
Case-Control	2008	Merritt	Int J Cancer	Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer	Ever/never use of talc in perineal region	1.17	(1.01, 1.36)
Case-Control	2009	Moorman	Am J Epidemiol	Ovarian cancer risk factors in African-American and white women	"Talc use" (Yes/No)	1.04 (White); 1.19 (AA)	(0.82, 1.33) White; (0.68, 2.09) AA
Case-Control	2009	Wu	Int J Cancer	Markers of inflammation and risk of ovarian cancer in Los Angeles County	"Ever" use of talc ("Ever" if used at least once per month for 6 months or more)	1.48	(1.15, 1.91)
Case-Control	2011	Rosenblatt	Gynecol Oncol	Genital powder exposure and the risk of epithelial ovarian cancer	Regular direct perineal powder application after bathing	1.27	(0.97, 1.66)
Case-Control	2012	Kurta	Cancer Epid Bio Prev	Use of fertility drugs and risk of ovarian cancer: Results from a U.S.-based case-control study	"Ever" use of talc in perineal region	1.4	(1.16, 1.69)
Case-Control	2012	Lo-Cignaic	Epidemiol	Aspirin, non-aspirin non-steroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer	Any genital talc use at least once per month for six months or more (*As reported in Terry 2013 pooled analysis, ref. 26)	1.34	(1.07, 1.66)
Case-Control	2015	Wu	Cancer Epid Bio Prev	African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic whites after considering nongenetic risk factors and oophorectomy rates	≥ 1 Year of genital talc use	1.46	(1.27, 1.69)
Case-Control	2016	Cramer	Epidemiology	The association between talc use and ovarian cancer - A retrospective case-control study in two US states	Any personal genital talc use	1.33	(1.16, 1.52)
Case-Control	2016	Schildkraut	Cancer Epid Bio Prev	Association between body powder use and ovarian cancer: The African American Cancer epidemiology study	Any genital powder use	1.44	(1.11, 1.86)
Case-Control	2021	Davis	Cancer Epid Bio Prev	Genital powder use and risk of epithelial ovarian cancer in the Ovarian Cancer in Women 2 of African Ancestry Consortium	Ever Use Genital Powder	1.32 1.36 (White); 1.22 (AA)	(1.17, 1.48) (1.19, 1.57) White; (0.97, 1.53) AA